British Journal of Anaesthesia

JOINT EDITORS:
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Volume XXIX No. 3 March 1957

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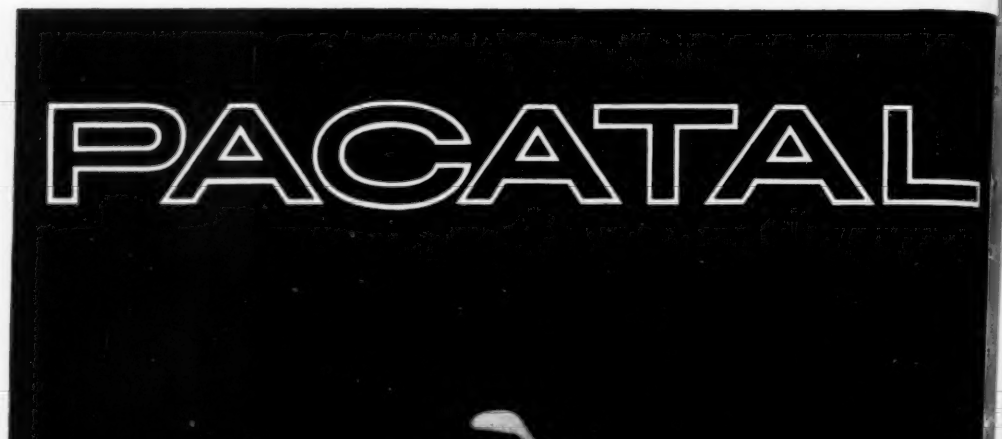

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BRITISH JOURNAL OF ANAESTHESIA

VOL. XXIX, No. 3 MARCH 1957

EDITORIAL

NEW DEPARTMENT OF ANAESTHETICS

THE establishment of a new Department of Anaesthetics within the Royal College of Surgeons cannot fail to give a new impetus to research in anaesthesia in this country. The standard of clinical anaesthetics in Britain over the country as a whole must be unique in the world. Already in five centres there are University Departments with considerable research facilities, and these together with the new department, which has the advantage of freedom from teaching and administrative commitments, should enable Britain to maintain its position in anaesthetic research.

The staff of the new department consists of the Director, Dr. Ronald Woolmer, a First Assistant (Dr. Gerald R. Graham), a Physicist (Mr. Dennis W. Hill) and a Research Fellow (Dr. John F. Nunn), as well as the usual technical and secretarial personnel. The Department occupies the 6th floor of the Nuffield College of Surgical Sciences which has been erected next to the main building of the Royal College of Surgeons. It covers an area of about 3,000 square feet. This is divided into a main laboratory, a subsidiary laboratory which can be used as an animal operating room, a well equipped workshop, a small reading room and a store room, as well as rooms for the Director and his staff.

The Department is in close proximity to the Department of Physiology, and when the College's rebuilding scheme is complete the Department of Pharmacology will also be in the vicinity.

The specialty can only be grateful to the foresight and generosity of the Royal College of Surgeons and to those industrial concerns who have enabled this new department to come into being. For our part, we wish it well and the great success which it deserves.

Brit. J. Anaesth. (1957), **29**, 98

A TIME-PHASED END TIDAL SAMPLER SUITABLE FOR USE DURING ANAESTHESIA

BY

J. F. NUNN AND A. C. PINCOCK

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IT is well known that disturbances of the respiratory acid-base balance may occur during anaesthesia. Severe CO_2 retention will lead to coma and respiratory depression, but in moderate degrees the signs are notoriously inconstant. Previous hypoventilation may be the only reason for suspecting CO_2 retention and unfortunately little help can be afforded by measurement of CO_2 tensions as this presents special difficulties under the conditions of anaesthesia.

The determination of the P_{CO_2} of arterial blood is complicated by the presence of nitrous oxide, which makes it impossible to use the direct method of Riley et al. (1945). Indirect determination from pH and CO_2 content is possible but the technique requires certain modifications (Orcutt and Waters, 1937) and is inevitably time consuming and laborious. Furthermore, the accuracy is limited by the slope of the CO_2 dissociation curve. It is possible that the method recently described by Astrupp (1956) will be applicable to the conditions of anaesthesia and will provide a means for the rapid and accurate determination of the arterial P_{CO_2}.

Alveolar gas analysis presents an alternative to monitoring the arterial blood. Again nitrous oxide interferes with many methods of gas analysis which may be used for CO_2, but the principal technical difficulty during anaesthesia is sampling. Eastwood and Harbord (1955) have described the collection of alveolar samples from unconscious patients after large passive expirations and Scurr (1956) has used the equilibration method of Plesch (1909) during anaesthesia, thereby obtaining values approximating to the P_{CO_2} of mixed venous blood.

A more satisfactory technique is the instantaneous analysis of expired gas by the mass spectroscope (Buckley et al., 1952; Woolmer, 1953) or by the rapid infrared gas analyzer (Fowler, 1949; Dubois et al., 1952; Siebecker, 1954; Elam et al., 1955). Not only is it possible to measure the alveolar concentration of CO_2 but, by inspection of the curve, it is possible to establish whether alveolar gas has in fact been sampled. It is unfortunate that rapid gas analysis involves considerable technical difficulties and such methods, while admirably suited to research, have at present little place in the routine care of anaesthetized patients.

It has been established by many workers that normally the P_{CO_2} of end tidal gas approximates closely to that of alveolar gas and arterial blood (Dubois et al., 1952). With end tidal sampling it is not necessary to use instantaneous methods of gas analysis and the technique is thereby greatly simplified. Terminal end tidal samples may be withdrawn manually by the method of Inkster and Rees (1956), but the automatic "through the valves" devices for end tidal sampling introduced by Henderson and Haggard (1925) and later developed by Rahn, Mohney, Otis and Fenn (1946) are generally unsuitable for use during inhalational anaesthesia. Not only is the instrument dead space too high for the reduced tidal volumes which may be encountered, but in most anaesthetic systems there is some admixture of expired gas with surplus fresh gas supply during the latter part of expiration. Suskind and Rahn (1954) have used a method of this type during intravenous anaesthesia.

Krogh and Lindhard (1914) used the volume of gas expired to actuate collection of samples from various fractions of expired gas. This principle was later used by Loeschke, Opitz and Schoedel (1939) who devised a volume phased

end tidal sampler to aspirate samples from the trachea after a certain volume had been expired. This method had the advantage of not sampling from short expirations, but it was particularly cumbersome and as the apparatus incorporated a spirometer it could not easily be adapted to artificial ventilation by intermittent positive pressure.

As most measurements of end tidal P_{CO_2} would be made in a steady state with constant tidal volume and respiratory frequency, the time required for the expiration of a predetermined volume should be reasonably constant. It thus appeared feasible to use a time delay so that sampling could be restricted to that time when alveolar gas occupied the region from which the sample would be collected. Time phasing would retain most of the advantages of volume phasing but would be more convenient in operation and could be made independent of any external breathing apparatus. In particular such a method could be used with most forms of anaesthetic apparatus and with intermittent positive pressure respiration.

The present study was therefore undertaken to determine the feasibility of obtaining alveolar samples with a time phased end tidal sampler. In addition, the colorimetric method of determination of carbon dioxide tension in a gas was investigated as it appeared to be a suitable method for use with the sampler.

Throughout this article the term "dead space" refers to anatomical dead space. This has recently been defined by Harris (1956) as that part of the respiratory tract which is filled with inspired gas at the end of inspiration and with alveolar gas at the end of expiration.

METHOD

The sampling mechanism is operated by the differential pressure which develops, during expiration, across the slight resistance afforded by the mouthpiece or the endotracheal tube connec-

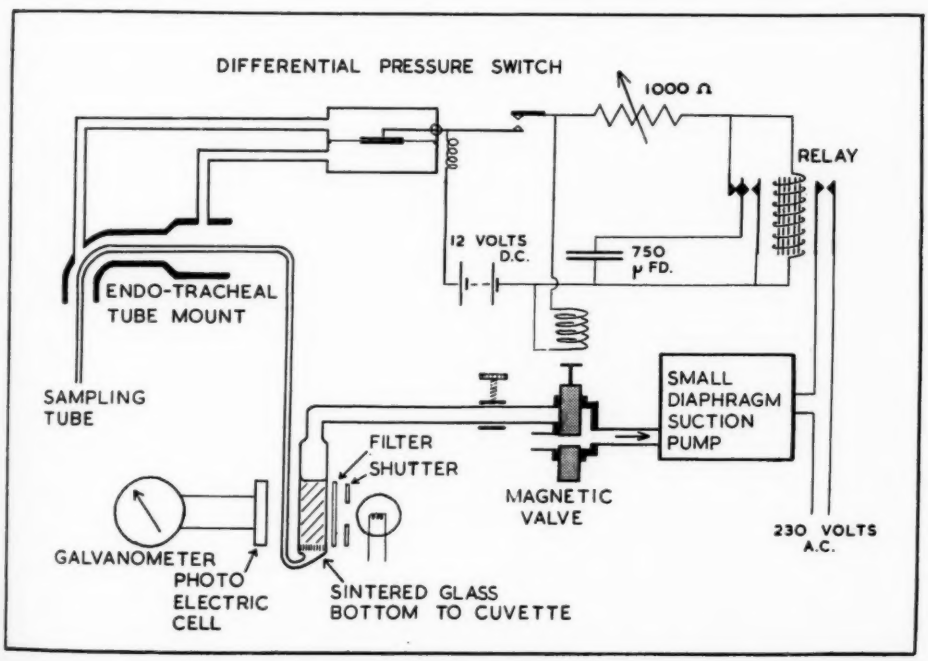

FIG. 1

Circuit of the time phased end tidal sampler and CO_2 analyzer.

tion. This pressure is independent of the actual tracheal pressure changes during respiration and is thus unaffected by the manner of the breathing—whether spontaneous or artificial with a positive pressure during inspiration. The differential pressure across a normal endotracheal tube connection containing a concentric sampling tube (2.5 mm o.d.) is of the order of 3 mm water during quiet breathing with a peak flow rate of 18 litres/min. This has been found to be sufficient to operate contacts by means of a differential tambour (fig. 1).

When the contacts are closed at the start of expiration a magnetically operated valve puts the sampling pump in communication with the analyzer through which gases will be drawn. Simultaneously a potential is applied to a relay through a variable resistance-condenser network so that the pause before the relay is closed is controlled by the resistance. When the relay eventually closes two sets of contacts are closed; one starts the sampling pump while the other discharges the condenser. At the end of expiration the differential pressure switch is opened and the magnetically operated valve brings the sampling to an abrupt end. By reversal of the pressure leads it is possible to sample during inspiration.

The CO_2 analyzer is similar in principle to that described by Brinkman and Lamberts (1952), in which the gas is brought into contact with a buffered solution of an indicator. A solution of 0.005 per cent bromthymol blue with 0.05 per cent sodium bicarbonate is used and this changes colour from blue to yellow according to the tension of CO_2 to which it is exposed. Equilibration takes place in a cuvette with a sintered glass bottom, below which the gas is introduced from a side tube. By this means the gas stream is broken up into fine bubbles, thereby accelerating the attainment of equilibrium.

The light transmission of the solution, using a yellow filter, is measured by a barrier-layer-type photo cell and a galvanometer. The side tube is not in the optical pathway and sampling may be interrupted for reading. Frothing in the cuvette causes dye to be absorbed on to the foam and a much higher rate of gas flow is possible if the inside of the cuvette is treated with a silicone antifoaming agent. Approximately 1 ml of gas is sampled each breath.

The polythene sampling tube has an internal diameter of 1.5 mm and is passed down the airway to a point as near the carina as possible. During inspiration a small quantity of the indicator descends through the sintered glass plate displacing gas backwards along the sampling tube. It is felt that this may prevent diffusion of inhaled gases into the open end of the sampling tube, which has been a source of error in the past (Bracken—personal communication).

ASSESSMENT OF THE METHOD

The phasing of the end tidal sampler was studied by simultaneous recording of ventilation and the aspiration of samples. Respiration was simulated with a reciprocating pump and recorded on a spirometer, while the sampling tube was connected to a tambour, the movements of which signalled the duration of sampling (fig. 2).

The speed of response of the CO_2 analyzer was studied by drawing alternately air and a mixture of 10.5 per cent CO_2 in air through the analyzer. The galvanometer deflection was noted every 15 seconds until equilibrium had been obtained. The phasing of the sampling was intermittent and similar to that which would be used during normal respiration.

The CO_2 analyzer was calibrated against a number of cylinders containing CO_2 mixtures up to 10 per cent, the composition of which had been determined by the micro method of Scholander (1947). Duplicate analyses were required to agree within 0.03 per cent. With zero galvanometer deflection when no light fell upon the cell, the deflection was noted when these mixtures were drawn through the cuvette under constant conditions of light intensity and photo-cell sensitivity. The barometric pressure and the temperature of the cuvette were noted.

Comparisons were made between the P_{CO_2} of end tidal samples measured by the analyzer and the P_{CO_2} of Haldane-Priestley (1905) end inspiratory alveolar samples which were analyzed by the method of Scholander. The alveolar samples were collected after the subject had reached a steady respiratory state as shown by the end tidal P_{CO_2}

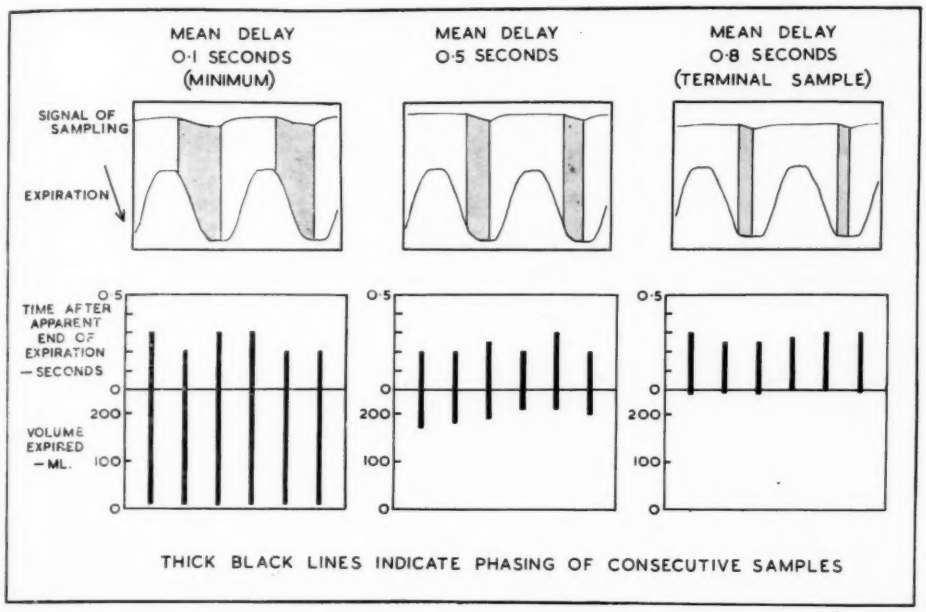

FIG. 2

Phasing of the end tidal sampler at various delays, with a tidal volume of 250 ml and a frequency of 24 b.p.m. For each setting of the delay tracings of two breaths are shown to illustrate the method and below these are records of the phasing of six consecutive samples. The lower part of each record indicates the volume expired before sampling commences, while the upper part indicates the time after the apparent end of expiration before sampling ceases.

The observations were repeated on the same subject at various tidal volumes which were obtained by varying the respiratory frequency while keeping the alveolar ventilation and P_{CO_2} at values not far removed from normal. Breathing was in time with a metronome and the tidal volumes were calculated from the minute volume which was measured with a dry gas meter. Simultaneous measurements of the alveolar and end tidal P_{CO_2} were plotted against the tidal volume.

The dead space of the subject was determined from Bohr's formula, using the concentration of CO_2 in the alveolar gas and the mean concentration in the expired gas which was collected in a Tissot spirometer for the measurement of the tidal volume.

RESULTS

With a constant tidal volume and respiratory frequency, it was possible to delay the commencement of sampling to any part of the expiratory phase (fig. 2). With maximum delay the sample was terminal and should correspond with the method of Rahn et al. (1946). With an intermediate delay it should be possible to sample mixed alveolar gas and obtain results similar to Loeschke et al. (1939). The persistence of sampling after the apparent cessation of expiration was inherent in the apparatus but did not exceed 0.25 seconds. Similar results were obtained during inspiratory sampling with the leads reversed.

The CO_2 analyzer showed 95 per cent response after 45–75 seconds and appeared to be little

influenced by the rate of aspiration of the sample (fig. 3).

The galvanometer deflections obtained during calibration with different tensions of CO_2 are shown in figure 4. Cuvette temperatures fell into three groups. It will be seen that while the effect of temperature was negligible with low tensions of CO_2, it was significant throughout most of the range of alveolar CO_2 tensions. In figure 5 the galvanometer deflections are expressed as a percentage of the deflection obtained with a gas of P_{CO_2} 36.0 mm Hg at the same temperature. The shaded areas include all the 54 points obtained during calibration between 21 and 28°C and suggest that with two fixed points—no light falling on the cell and the deflection at P_{CO_2} 36.0 mm Hg—the calibration curve is reasonably constant at the various temperatures. The maximum error from the mean is ±0.5 mm Hg up to P_{CO_2} 50 mm Hg and ±3mm Hg at P_{CO_2} 70 mm Hg.

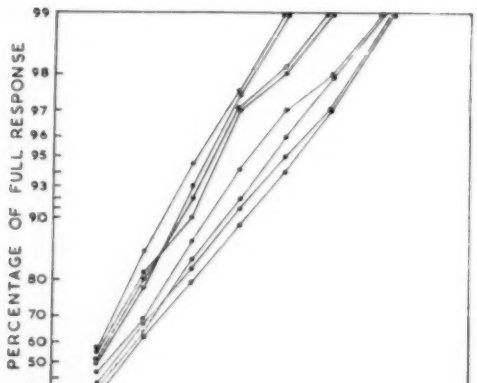

FIG. 3

Percentage response of the colorimetric CO_2 analyzer to step changes in P_{CO_2} of the sampled gas.

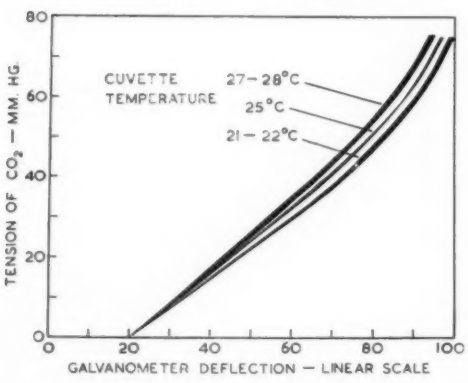

FIG. 4

Calibration curves of the colorimetric CO_2 analyzer at various temperatures, with constant intensity of light source. The shaded areas include all points obtained within the specified limits of temperature.

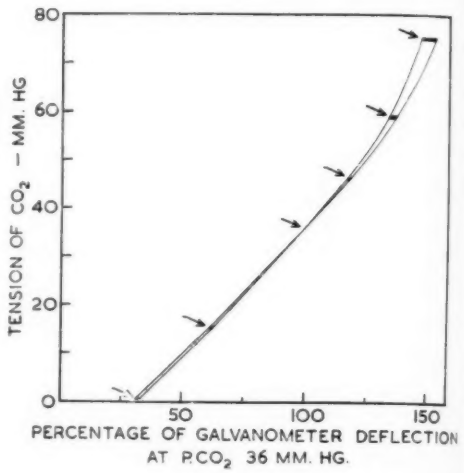

FIG. 5

Calibration of the colorimetric CO_2 analyzer expressed as a percentage of the galvanometer deflection at a P_{CO_2} of 36 mm Hg over a temperature range of 21 to 28°C. The shaded areas indicated by the arrows include all the points obtained.

The comparison with alveolar samples (fig. 6) shows that, in the present study, above a tidal volume of 300 ml (b.p.t.s.) the difference between the P_{CO_2} of Haldane-Priestley end inspiratory alveolar samples and end tidal samples analyzed by the colorimetric method did not exceed 2 mm Hg, which is within the combined error of the two methods. The mean alveolar P_{CO_2} exceeded the mean end tidal P_{CO_2} by 0.4 mm Hg (standard deviation 1.3 mm Hg). Below a tidal volume of 300 ml progressively

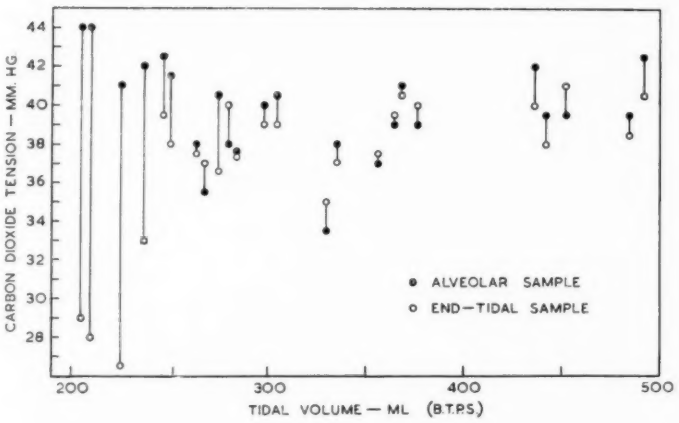

FIG. 6

Simultaneous determinations of alveolar and end tidal P_{CO_2} at various tidal volumes. The dead space of the subject was 150 ml.

larger divergencies occurred until at 200 ml the difference was of the order of 15 mm Hg.

The dead space in the sitting position was found to be 150 ml. This is in accord with a body weight of 143 lb (65 kg) as shown by Radford (1955).

DISCUSSION

The results indicate that, with a constant tidal volume and respiratory frequency, it is possible to use time phasing to delay sampling until a reasonably constant volume has been expired. Due to the inertia of the apparatus sampling continues approximately 0.25 seconds after the apparent end of expiration, but it is unlikely that inspiration will commence within this period. During anaesthesia and intermittent positive pressure ventilation (for which this apparatus was particularly designed) the respiration is generally slow and there is also a postexpiratory pause. In addition, the dead space distal to the sampling point at the carina will normally contain alveolar gas which will pass the sampling point a second time during early inspiration.

The sensitivity of the pressure switch may be increased under certain conditions by allowing one side of the tambour to communicate with the atmosphere and actuating the mechanism with either a positive or negative airway pressure.

The colorimetric method of CO_2 analysis has the advantages of simplicity and lack of interference by other gas—particularly nitrous oxide. The response time is, however, slow and breath-to-breath changes in P_{CO_2} cannot be detected. Rather will the method indicate the mean end tidal P_{CO_2} over the previous minute, which is generally adequate during clinical use.

The calibration curve is reasonably constant at different temperatures and is almost linear up to a P_{CO_2} of 55 mm Hg. It is necessary to refer to a standard gas mixture at frequent intervals until thermal equilibrium has been obtained within the cuvette. Thereafter the stability is good and reference every 20 minutes is sufficient. Small cylinders of 5 per cent CO_2 in oxygen are suitable for use as standards, as not only are they readily available but their P_{CO_2} lies somewhere near the middle of the range encountered during anaesthesia. The contents may differ considerably from the composition claimed by the manufacturers and it is necessary to analyze the contents of each cylinder which is used for calibration.

It is convenient to prepare a direct reading scale for the galvanometer, and in this may be incorporated a correction for gases which, when sampled, are saturated with water vapour at body temperature.

There is close agreement between end tidal

samples and Haldane-Priestley end inspiratory alveolar samples at normal tidal volumes. However, there is a discrepancy below a tidal volume of 300 ml when the volume expired is insufficient to wash out the dead space. This defect can be reduced by sampling from the carina if an endotracheal tube is in use. Lilly (1946) has referred to the expired volume required to wash out the dead space as the kinetic dead space, and Fowler (1948) found this to be of the order of 325 ml when the anatomical dead space was 156 ml. The present study is in reasonable agreement with these figures and it would appear, in general, that a tidal volume of at least double the anatomical dead space is required for sampling alveolar gas at the end of expiration. When sampling from the carina, a tidal volume of 140 ml should normally be adequate, since the work of Fowler and Blakemore (1951) and Folkow and Pappenheimer (1955) suggests that only one-third of the dead space is below the carina.

End tidal sampling in the presence of a defect of gas mixing was demonstrated in a patient with emphysema who was being ventilated by intermittent positive pressure during an attack of bronchopneumonia. The P_{CO_2} of the end tidal samples was compared with instantaneous analysis of the expired gas (fig. 7). It will be seen that the normal plateau of CO_2 in the alveolar gas was replaced by a steep gradient and although the end tidal sample represented the mean value on the gradient no expired gas approached the P_{CO_2} of the arterial blood which was determined simultaneously by the method of Riley et al. (1945). Under these conditions no gas analysis technique can reveal the true state of gaseous acidosis or alkalosis and there is no alternative to the analysis of arterial blood.

The results have shown that under normal conditions time phased end tidal samples had a P_{CO_2} closely approximating to alveolar gas and therefore to arterial blood. However, there are three factors which must be considered in the light of these results. First, the phasing of a sample must correspond to the alveolar fraction of the expired gas and must not be contaminated with dead space gas. Secondly, it must be known that the tidal volume is sufficient to wash out the dead space up to the point from which the sample is withdrawn. Thirdly, a defect of gas mixing

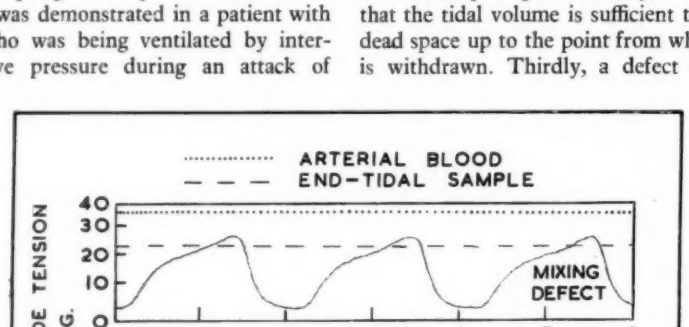

FIG. 7

P_{CO_2} of expired gas (determined by instantaneous analysis) compared with an end tidal sample collected concurrently. In the upper tracing the patient had a known mixing defect. In the lower tracing mixing was probably normal. In both cases the delay before sampling corresponded to approximately half the tidal volume.

associated with under perfused areas of the lung may introduce a gradient between the arterial and the end tidal P_{CO_2}. The arterial P_{CO_2} will usually be higher than the end tidal P_{CO_2} and this information may be of value.

When there is no reason to suspect that the end tidal tensions differ from the arterial, time phased end tidal sampling offers a simple and convenient method for monitoring changes in P_{CO_2} and figure 8 is a typical example of the continuous estimations of P_{CO_2} which are possible. The method has been used extensively with various anaesthetic techniques and also during the recovery phase. It has proved valuable in the treatment of prolonged respiratory failure by cabinet-type respirators and by intermittent positive pressure ventilation. It has also been of use for the determination of the alveolar P_{CO_2} in normal subjects breathing through mouthpieces and for the investigation of the inspiratory CO_2 concentration in various types of breathing apparatus.

SUMMARY

(1) A method of end tidal sampling is presented, in which alveolar gas is obtained by delaying sampling during the expiratory phase with a variable condenser-resistance network. The CO_2 tension of the samples is determined continuously with a colorimetric analyzer.

(2) In the normal subject the P_{CO_2} of the samples agrees closely with the P_{CO_2} of Haldane-Priestley end inspiratory alveolar samples, provided that the tidal volume is sufficient to wash out the dead space.

(3) Practical applications of the technique are outlined.

FOOTNOTE

Further development work for the commercial production of this apparatus is being carried out in conjunction with the medical division of Stanley Cox Ltd.

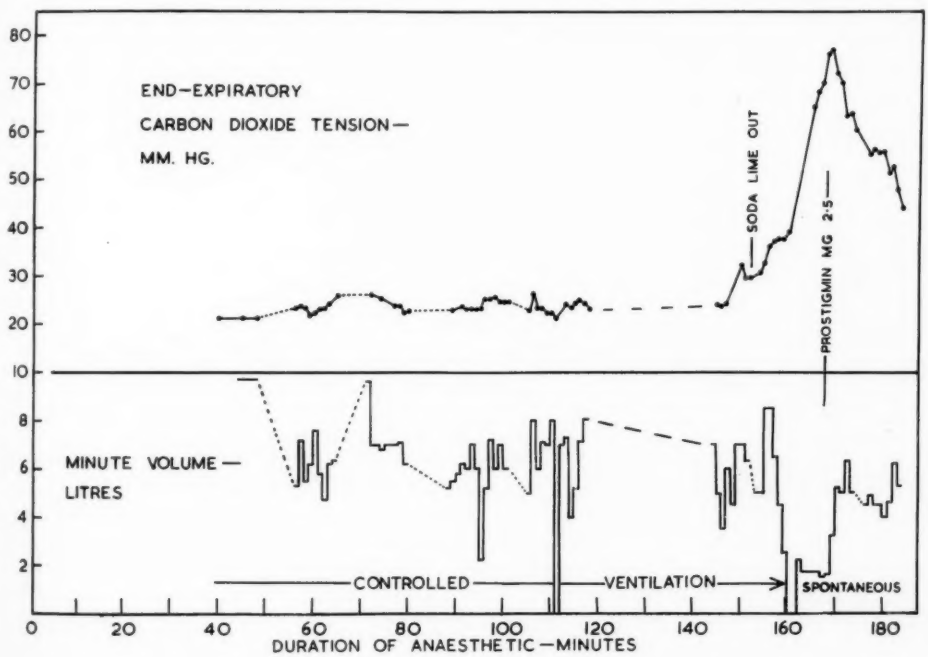

FIG. 8

Monitoring of end expiratory P_{CO_2} during mitral valvotomy. Anaesthesia: thiopentone, curare, and pethidine, with nitrous oxide and oxygen administered in a circle system with soda lime.

ACKNOWLEDGMENTS

We are indebted to a grant from the endowment Research Fund of the United Birmingham Hospitals and to Professor F. A. Stammers, Mr. A. L. d'Abreu, Dr. B. L. S. Murtagh and other members of the hospitals for facilities for clinical trials. We are also indebted to Professor W. M. Arnott for his encouragement and help and to Dr. J. Butler for his assistance in preparing the manuscript.

It is again a pleasure to thank Mr. H. A. Crisp for the construction of the apparatus.

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Brit. J. Anaesth. (1957), **29**, 107

A METHOD OF ANAESTHESIA FOR THORACOTOMY IN EXPERIMENTAL ANIMALS

With Special Reference to the Study of Oesophageal Activity

BY

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DIRECT observation of oesophageal motility in man and animals has been rendered difficult by the problem of exposure without interfering with swallowing and peristalsis. Although thoracotomy is an everyday procedure in the human subject, it is still hazardous in small animals. Furthermore the usual methods of thoracic anaesthesia either abolish or markedly affect oesophageal motility; the use of relaxants would vitiate any investigation of the part played by striated muscle.

In order to study the physiological activity of the entire oesophagus visually, our anaesthetic technique should fulfil the following conditions:

(1) The animal would be certain to remain unconscious when respiration was abolished and the normal signs of anaesthesia were no longer evident.

(2) Neither a myoneural blocking agent nor profound general anaesthesia should be used.

(3) Satisfactory gaseous exchange should be maintained for as long as may be necessary.

METHOD

In most animal work it is both convenient and humane to induce anaesthesia with a barbiturate or bromethol given either intravenously or into the peritoneal cavity. This secures basal narcosis but for traumatic procedures additional anaesthesia will be required. Eighty per cent nitrous oxide with oxygen, is probably the ideal agent but must be administered without air; this is difficult if an endotracheal tube cannot be used since a close fitting mask presents a problem in animals. Controlled respiration is generally regarded as essential when the pleural cavity is opened; it can be initiated in three ways (Lee 1953):

(1) The threshold of the respiratory centre to carbon dioxide may be raised by deep general anaesthesia.

(2) The level of carbon dioxide in the body may be reduced below the respiratory threshold.

(3) The voluntary muscles may be paralysed by a myoneural blocking agent.

Wright (1956) recommends, for larger animals, hyperventilation after obtaining basal anaesthesia with pentobarbitone. In all the species in the present investigation it was not difficult to reduce the carbon dioxide tension by a short period of controlled hyperventilation; apnoea then supervened and could be maintained indefinitely by moderate hyperventilation. Spontaneous respiration returned promptly if the ventilation was reduced or stopped. Provided that an adequate concentration of nitrous oxide was maintained the animal would remain unconscious, even after the basal anaesthetic had worn off.

For controlled ventilation we have used a simple T-piece arrangement (fig. 1). Although this is wasteful in the larger animals and man, it is quite economical in the smaller experimental animals. It has the advantage of simplicity in construction, maintenance and use. There is no rebreathing, no necessity for soda lime, and the dead space is reduced to a minimum. The constituent parts are all standard anaesthetic equipment for the gas supply from cylinders fitted with Adams reducing valves giving a pressure of 250 mm Hg. This is higher than necessary and may be undesirable since over distension and rupture of the lungs could occur should inflation be unduly prolonged; in practice, however, it is simple to limit the phase of inflation to produce

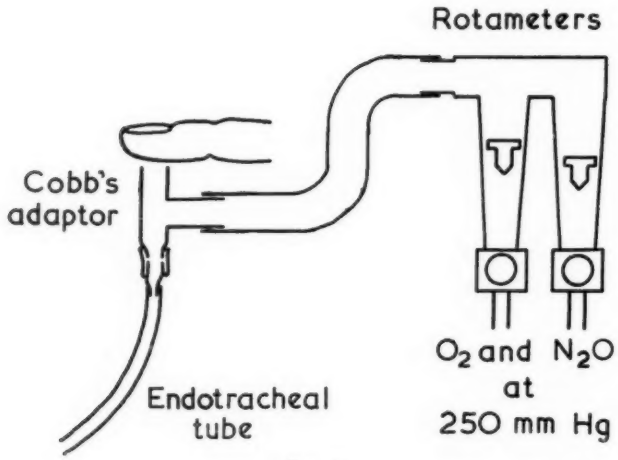

FIG. 1
Apparatus for controlled ventilation of small animals.

any required degree of lung expansion. Provided the flow rate of the fresh gas supply is reasonably low and the open limb of the T-piece is occluded for only the minimum time, there should be no excessive build up of intrapulmonary pressure; it is possible to fit a safety valve to prevent any possibility of high inflation pressure. The method is easier to manage when the gas flow in small animals is reduced.

The following flow rates were found to be suitable: rabbit 1.5 l./min; guineapig 1.0 l./min; mouse 0.5 l./min.

Usually 80 per cent nitrous oxide in oxygen was used in all species.

PROCEDURE

Pre-operative starvation is desirable in survival experiments: a full stomach has never affected our results in acute experiments. Atropine and morphine depress oesophageal activity and were not therefore used for premedication. No difficulty was encountered from salivary and bronchial secretions.

Induction.

After weighing, each animal received a basal anaesthetic—in the bigger animals intravenous or intraperitoneal veterinary pentobarbitone (Nembutal) 26 mg/kg body weight. Intravenous administration produces a rapid onset of anaesthesia facilitating immediate intubation. In smaller animals a 1 in 20 solution of bromethol in amylene hydrate was used intraperitoneally (80 mg/kg body weight). The dosage of these drugs in animals is extremely variable and the full dose often produces unpredictable results; it was, therefore, found to be safer to supplement a small initial dose, if necessary.

Intubation.

Intubation without relaxants presented no difficulty in any of the species studied. Blind intubation is easy, but may be traumatic, especially in the smaller animals when it may interfere with the swallowing reflex; therefore a Shadwell infant laryngoscope was used at first, but one of us (G.S.M.B.) designed a modification that was better adapted to the long narrow palates of the smaller animals (fig. 2). Standard Magill endotracheal tubes were used: dogs need large cuffed tubes: intubation was impossible in the smaller species like the mouse, rat and guineapig, and tracheostomy was performed using thin rubber or polythene tubes. The greatest care had to be taken to avoid injury to the motor nerves of the oesophagus during tracheostomy. It is important to ensure that the animal cannot occlude the tube should the bite reflex return before the tube

FIG. 2
Special laryngoscope to facilitate intubation in the smaller species.

is removed; a metal guard over the endotracheal tube is a safeguard which should always be used.

Maintenance.

The incision was made, and any associated abdominal procedure completed with the animal breathing spontaneously either air or nitrous oxide and oxygen. Haemostasis is of considerable importance in smaller animals in view of their small blood volume. Carbon dioxide was reduced by vigorous hyperventilation as the chest was about to be opened: apnoea followed after a few breaths and the pleura was then opened. Ventilation was then controlled at a rate sufficient to keep the carbon dioxide level below the respiratory threshold. One lung could be collapsed completely by deliberately passing the endotracheal tube into the opposite bronchus; this facilitated exposure and reduced the number of retractors required in a very confined area. The depth of anaesthesia could be altered within fine limits by changing the concentration of nitrous oxide.

At the conclusion of operation, if the animal is to survive, there should be no residual pneumothorax; the lungs must therefore be fully inflated when the chest wall becomes airtight. Pleural closure is difficult in small animals and care must be taken not to damage the lungs for a bronchopleural fistula is serious; intercostal drainage is not practicable in small species.

DISCUSSION

This technique has been used for the mouse, hamster, rat, guineapig, ferret, rabbit, cat, monkey, pig and dog. The dose of the basal narcotic, the size of endotracheal tube and the total gas flow varied with species. The low total gas flow in small animals not only provided a very economical anaesthetic technique, but also decreased the possibility of overdistension of the lung parenchyma. One of us performed the intubation (or tracheostomy) but thereafter the anaesthetic could be left in the hands of a technician; the great majority of the experiments were performed with only one assistant. Apart from the basal narcotic, the only physiological transgression was the low carbon dioxide tension with associated respiratory alkalosis and possible changes in serum electrolytes and regional blood flow. There was no apparent interference with oesophageal function and primary peristalsis could be initiated by squirting water into the pharynx. Secondary peristalsis was studied by

introducing balloons into the oesophagus. Oesophageal motility was seen in some species while in others the lightest possible phase of anaesthesia had a depressant action on the physiology of the organ.

The general condition of the animals appeared satisfactory. Those which were intended to survive recovered well and anaesthesia was maintained in the nonsurvival experiments for as long as four hours.

SUMMARY

(1) An anaesthetic technique is described which can be used conveniently for thoracotomy in many different experimental animals.

(2) Although based on current practice in the human subject, no relaxants are used.

(3) The apparatus is simple and maintenance of the anaesthetic can be carried out adequately by a technician.

(4) Motility of the cervical, thoracic and abdominal oesophagus can be studied directly.

ACKNOWLEDGMENTS

We wish to thank Mr. B. N. Brooke for valuable suggestions and Mr. T. F. Dee, Clinical Photographer to the Queen Elizabeth Hospital, for the photographs.

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BOOK REVIEWS

Exposés d'anesthésiologie a l'usage des praticiens et des étudiants. By P. Huguenard and P. Jaquenoud. Published by Masson et Cie, Paris. Pp. 200.

It would be difficult to compress more useful knowledge into the 200 pages of which this small volume consists than has been done by the authors Messieurs P. Huguenard and P. Jaquenoud. It begins with an all too short glossary of terms used in the text, this is followed by an example of how to examine and report on a patient who has submitted himself for operation. The authors suggest that the ability to make a report is one of the best tests of a candidate's ability to become a good anaesthetist; certainly if he will master pages 15–25 of this small book, the implications thereof, and put them into practice, he will be well on his way.

Next we come to the problems posed to the anaesthetist by the nature of the operation or of the condition of the patient, for example, the neurosurgical, the abdominal urgency, the badly burned or the diabetic, etc. Two chapters, one on pharmacology and the other on physiology, follow, both dealing with aspects which are very much to the fore just now. The book concludes with a description of a few techniques—how to introduce a tube into the trachea, a catheter into a vein or put a dog to sleep, and an "Extrait du règlement des concours de l'assistance publique a Paris."

Acta de l'institut d'anesthesiologie. Tome V, 1956. Published by Librarie Arnette Paris. Pp. 250.

This volume of some 250 pages is divided into two parts. The first gives the seven lectures of the "Cours supérieur d'anesthésie" for 1955–56. Such exciting subjects as "Postoperative pain", "Causes and treatment of cardiac arrest during operation", "Indications for tracheotomy" and the "Early treatment of burns" will interest all our readers. General anaesthesia in dentistry and the distribution of water as it varies in the adult and the child will make a more limited appeal. How, where and when to make intra-arterial injections and the complications that may follow is the subject dealt with by Louis F. Hollender of Strasbourg and is well worth the attention of every anaesthetist.

The second part consists of eleven papers dealing with subjects constantly in the mind of the anaesthetist, such for example as the measurement of CO_2 during anaesthesia, a new cardiac reanimator and the influence of drugs on anoxia.

E. Falkner Hill

Brit. J. Anaesth. (1957), **29**, 111

THE CEREBRAL EFFECTS OF OVERVENTILATION

(Preliminary Communication)

BY

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IT is a common observation among anaesthetists that overventilation appears to increase the depth of anaesthesia produced by any given dose of an anaesthetic agent. Many anaesthetized patients are overventilated for this purpose and also to avoid the dangers of underventilation, particularly when relaxant drugs are used. It seemed of interest to investigate whether overventilation could truly augment anaesthesia, or whether it only appeared to do so by reducing the respiratory activity of the patient. If an increase in depth of anaesthesia was proved it would obviously be important to find out if this was harmless.

One of the first effects of most anaesthetic agents is to produce some general analgesia, so it seemed that comparing the pain threshold under normal conditions and in the hyperventilated subject might be of value. Such a comparison has been made on myself and on others using the following technique.

The pan on the top of a household spring balance reading 0 to 20 lb (0 to 9 kg) was removed and replaced by a roundheaded screw. It was found that applying the head of the screw with increasing pressure to the anterior surface of the tibia of a conscious subject would cause a sense of pressure which would suddenly change to one of pain. When this change occurred the pressure being applied was read off the scale. A reading, constant to within about a pound, was obtained over the length of the tibia, provided that the extremities in the region of the knee and ankle were avoided. Presumably this was because of the greater amount of subcutaneous fat in these areas.

The psychogalvanic reflex (i.e. the change in skin resistance that occurs with certain stimuli) was recorded during one of these experiments and was found to be initiated at the same moment as the pain reading on the spring scale, which suggests that this may be an accurate method of measuring the pain threshold. It is simple and can give moment-to-moment readings.

The normal pain threshold measured with this instrument lay usually between 6½ and 9 lb (3 and 4 kg) in various subjects. The readings (table I) taken during forced breathing rose steadily to a value of 14 to 17 lb (6 to 8 kg),

TABLE I

Readings in pounds taken at ½-minute intervals.

Subject R.	Normal respiration	6½	7½	7½	7½	7½	8	7	
	Forced respiration	7½	9	8	10	9½	11½	11½	
	Degree of overventilation obviously not very great despite encouragement to continue.								
Subject W.	Normal respiration	10	10	10	9½	9	9		
	Forced respiration	9	14	16	14	17			
Subject C.	Normal respiration	8	8	7½	7½	7	8		
	Forced respiration	8	12	12	10	12	13	13	14
Subject E.	Normal respiration	6½	6½	7	8	7¼	7¼		
	Forced respiration	7	7	10	10	13	14		
Subject N.	Normal respiration	7½	7½	7½	7½	7	7		
	Forced respiration	8	7	10	10	10	10		
	Experiment abandoned because of pallor and discomfort of subject.								
Subject C-B.	Normal respiration	6½	6½	7	6½	7	7		
	Forced respiration	6½	8½	11½	14				

in two or three minutes, if the subject could be persuaded to continue overbreathing despite the discomfort produced.

This experiment was repeated with an arterial tourniquet round the thigh and the same effect was produced, so presumably the cause must lie centrally and not peripherally. The subject in these experiments was recumbent.

It seems that overventilation will cause some degree of general analgesia which could presumably potentiate the effect of an anaesthetic agent. The mechanism whereby this happens must next be investigated. Kety and Schmidt (1946) have shown that quite moderate degrees of overventilation would reduce the cerebral blood flow on the average to two-thirds and in one case to one-half of the original value. They found that the total oxygen uptake by the brain was not reduced, the venous blood being much less oxygenated than normal. They estimated that because of this low venous oxygen tension the cerebral cortex was in equilibrium with an oxygen tension equivalent to the subject breathing 6–8 per cent of oxygen. I found that breathing 8–10 per cent oxygen would raise the pain threshold to the same degree as would moderate overventilation, which agrees well with the 6–8 per cent O_2 estimated by Kety and Schmidt.

These experiments suggest that cerebral hypoxia may be produced by overventilation, though this is difficult to reconcile with the unchanged oxygen uptake. A possible explanation for this is suggested later. It might be thought that this question of hypoxia could be resolved by electroencephalography, but the slow wave response to overbreathing is nonspecific and there are many factors including the inherent stability of the subject (Morrice, 1956).

To investigate possible cerebral hypoxia the pain threshold of the subject was again measured, this time while he overventilated through a non-rebreathing system consisting of the two valves and the expiratory and inspiratory tubes of a circle absorption apparatus. No anaesthetic agents were, of course, being employed. When the expected rise of the pain threshold to 14 lb (6 kg) occurred a large flow of oxygen was blown into the inspiratory side of the apparatus and the subject continued to overventilate. The pain threshold fell nearly, but not quite, to normal, i.e., to 9 lb (4 kg) when the normal reading was 7 lb (3 kg) (fig. 1). Overventilation with oxygen was continued until after four minutes the subject was in a state of incipient tetany with risus sardonicus and carpopedal spasm. The pain threshold remained slightly raised. This suggests that the analgesia produced is caused by cerebral hypoxia and not by the lowered CO_2 tension. This hypoxia might be caused by the reduction in the cerebral circulation or, in part, by a shift to the left of the haemoglobin dissociation curve.

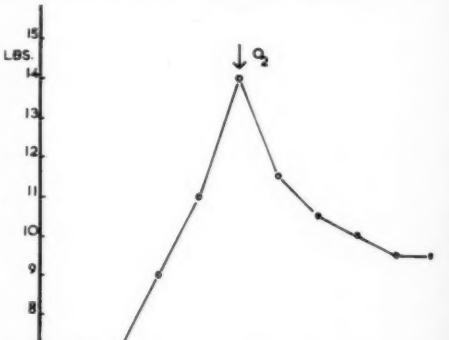

FIG. 1

The effect of oxygen on the rise in pain threshold produced by overventilation.

To differentiate between these two possible causes overventilation was again performed by a conscious subject; and when the pain threshold rose to the 14 lb (6 kg) mark the vapour of amyl nitrite was inhaled while overventilation continued. The pain threshold fell sharply to normal (fig. 2). Subjectively the brain was felt to clear though the paraesthesiae remained unchanged. The pain threshold under normal conditions I have found to be unaffected by amyl nitrite provided the subject was lying down. If he is sitting up the pain threshold rises with fall in blood pressure. It would seem, therefore, that the hypoxia is due to cerebral vasoconstriction. How then can we explain the failure of this vasoconstriction and lowered oxygen tension to cause a

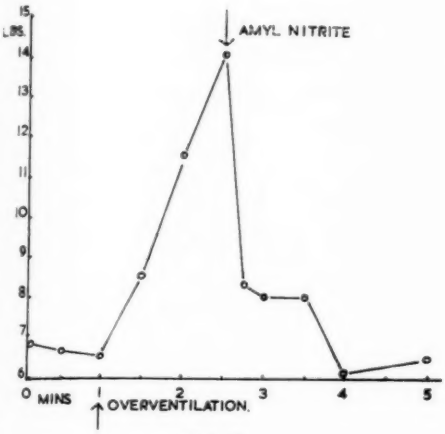

FIG. 2

The effect of amyl nitrite on the rise in pain threshold produced by overventilation.

reduction in the total uptake of oxygen by the brain?

It has been shown by Kugelberg (1948) that human nerves can be stimulated into spontaneous activity by overventilation. It would seem possible then that overventilation might increase the spontaneous activity of the brain and hence its oxygen requirements. Thus there might be a relative hypoxia under these conditions. Alternatively it may simply be that the change in oxygen tension is insufficient to alter the uptake. Whatever the explanation it seems doubtful that we should deliberately overventilate a patient and so run the risk of cerebral hypoxia. The effect is probably unimportant in the young and fit, though it might militate against recovery after severe operations on the frail and old, whom I have found particularly easy to overventilate during anaesthesia for abdominal surgery.

It is interesting to reflect that overventilation causes analgesia and that pain causes overventilation. A child will cry with pain and thus will overventilate. I have found, too, that in some cases it is impossible to stop, by overventilation, respiratory efforts in the lightly anaesthetized and partially paralysed patient where there is much painful stimulus from the operation.

There is evidence that overventilation adversely affects other parts of the cardiovascular and nervous systems, and experiments are continuing, but it was thought, in view of the common practice of overventilation, that anaesthetists would be interested in a short account of some of the experiments that have been performed.

SUMMARY

Experimental evidence is produced which suggests that the cerebral vasoconstriction produced by overventilation may cause hypoxia and should be avoided.

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Brit. J. Anaesth. (1957), **29**, 114

POSTOPERATIVE VOMITING

Some factors affecting its incidence

BY

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INTRODUCTION

NAUSEA, retching and vomiting have been distressingly common since the earliest days of surgical procedures carried out under general anaesthesia. During the last century there have been almost as many remedies suggested for postoperative vomiting as there have been reasons brought forward for its occurrence.

Remedies in the past have been dietetic, medicinal, symptomatic and psychological, including such treatments as meat free diets (Kemp, 1936), administration of glucose and insulin (Minnitt, 1933; Smith, 1934), Lugols iodine (Kemp, 1936), pyridoxine, chloretone, black coffee, iced water (Hewer, 1953). Even the application of mustard leaves to the epigastrium as a counter irritant has been tried.

In 1883 Brown Sequard noted that vomiting following morphine administration could be ameliorated by the addition of atropine and about the same time Professor Fraser of Edinburgh noted that atropine also decreased vomiting associated with chloroform anaesthesia (Duncum, 1947).

However, it was not until the introduction of the ultra short acting barbiturates in the 1930s that marked progress was made in reducing postoperative vomiting, and more recently still the antihistamine drugs, particularly the phenothiazine derivatives, have made severe vomiting uncommon after anaesthesia.

Many authors have published figures in the last twenty years of the incidence of postoperative vomiting. In a survey of over 10,000 patients Waters (1936) quoted a vomiting rate of 40.6 per cent. Davies (1941) in a series of 1,000 cases gave his vomiting rate as 44 per cent.

More recently Rubin and Metz-Rubin (1951), Albert and Coakley (1954), Dent et al. (1955), Knapp and Beecher (1956) have given figures for vomiting rates before administration of antihistamines varying from 75 to 27 per cent and after antihistamines these figures were reduced to between 45 and 13 per cent.

There is a wide variation in the figures quoted and this may be due to the varying premedicant and anaesthetic drugs used, the patient's age, sex, the length and severity of operation, as well as the different methods of assessing postoperative nausea and vomiting.

The very large number of factors involved in initiating the vomiting reflex postoperatively suggests the most obvious method of control to be the interruption of the reflex arc at the vomiting centre by depressant drugs acting upon this centre.

The object of this survey was to study 2,500 cases pre- and postoperatively to assess the more important factors that affect the incidence of postoperative vomiting in this hospital and attempt to lower this incidence without prejudicing the patient's recovery.

METHOD

The investigation was carried out in two parts. First approximately 1,700 unselected routine cases for surgery under general anaesthesia were taken and detailed records were kept of each operation and anaesthesia (fig. 1). These cases were to be used as controls to assess the current incidence of nausea and vomiting following operation in this hospital. The second half of the investigation was similar in all respects except that either promethazine or chlorpromazine was added to the premedication. A proforma was prepared (fig. 1). The procedure was that part I of the form was made out for each patient in the ward and brought to

the theatre with the patient. The anaesthetist filled in part II of the proforma after each case or at the end of each operating session. The cases were interviewed by one of us (each seeing the other's cases) between 24 and 36 hours postoperatively and part III of the proforma completed.

The information thus recorded was transferred in the hospital's Record's Department to Hollerith cards and the statistical information was obtained by machine (Power Samas) at the end of the investigation.

The patients when interviewed, were asked whether they had had any nausea or vomiting, the duration of the symptoms and the number of times they had been sick. The nursing staff kept records of the observed vomiting.

CRITERIA

Nausea lasting continuously or intermittently up to 4 hours at any time during the first 24 hours was classed as " slight ", and anything more than this as severe. Originally, as can be seen from figure 1, the vomiting was to be classed as slight, moderate and severe—severe being any vomiting lasting persistently over 12 hours—but this was so rare that the " moderates " and " severes " were combined in the final analysis for the sake of simplicity.

Vomiting, both subjective and objective, was divided into " slight " if it occurred on not more than four occasions, and more than this was recorded as " severe ".

The assessment of nausea and vomiting was not easy as the patient's time sense and memory was not always accurate immediately postoperatively. However, the incidence of subjective and objective vomiting was very similar. Occasionally a patient would be amnesic for a bout of vomiting that had occurred shortly after return from the theatre, and on the other hand, some patient's assessment of subjective vomiting was considerably higher than that observed. Nausea was never classified as being less than the subjective vomiting as nausea is almost invariably felt prior to the act of vomiting.

No attempt was made to influence the anaesthetist's choice of premedication or anaesthetic during the control phase of the survey, but in the second half of the investigation the anaesthetists were asked to incorporate promethazine or chlorpromazine into the premedication in 25-50 mg dosage, usually the latter, either orally 2-4 hours pre-operatively, or intramuscularly with the routine premedication 1 hour pre-operatively.

These drugs were in fact prescribed for some patients during the first half of the investigation either because of bronchospasm or a history of previous severe postoperative vomiting. These cases were included in the final analysis in the Antihistamine Group and not in the Control Group.

A number of cases were not included in the survey; those dying within 24 hours of operation were excluded. Emergencies admitted at night were often missed. The record forms were sometimes lost, defaced or inaccurate and these were discarded. Those patients who were nauseated or who were vomiting either before or after premedication, but before induction of anaesthesia were dealt with separately (table I). In children under 10 years old nausea and subjective vomiting were recorded as

TABLE I

Analysis of all cases into the three main groups and those excluded from them.

	Cases	Nausea		Subjective vomiting		Total	Objective vomiting		Total
		Slight	Severe	Slight	Severe		Slight	Severe	
		%	%	%	%	%	%	%	%
Control cases	1702	25.8	10.5	23	8.8	32	23.7	7.9	32
Promethazine cases	490	23.3	4.1	14.7	3.3	18	16	2	18
Chlorpromazine cases	111	7.2	9.1	10	5.4	15	12.6	5.4	18
Vomiting before operation	61	36	32.8	32.8	31.2	64	36	23	59
Ryle's tubes	156	26.6	8.3	10.1	2.6	13	10.9	2.6	14
Others (promethazine and chlorpromazine)	8	—	—	—	—	—	—	—	—
Totals	2528	24.6	9.6	20.3	7.7	28	21.2	6.8	28

THE MIDDLESEX HOSPITAL, W.1

POST-OPERATIVE VOMITING RECORD

DATE.....

I

NAME	Hospital No.						Sex and Age M : F	7	8
		2	3	4	5	6			
SURGEON	9	10	Anaesthetist				11 12 Ward	13	14
OPERATION	15	16	17	18	19		Secondary Diseases of interest		20

II

PRE-OPERATIVE VOMITING 21
None 0
Before premedication 1
After 2

PREMEDICATION 22

Morphia	1	Promethazine	5
Omnopon	2	Chlorpromazine	6
Pethidine	3	Atropine	7
Barbiturates	4	Scopolamine	8
		Other	9

INDUCTION 23

Easy	1	Spasm	4
Vomiting	2	Cyanosis	5
Swallowing	3	Carbon Dioxide used	6

RYLES TUBE 24
Yes 1
No 0

ENDOTRACHEAL TUBES 25

Oral	1	Cuffed	4
Nasal blind	2		
vision	3		

POSTURE 26

Supine	1	Lithotomy	4
Prone	2	Trendelenberg	5
Lateral	3	Reversed Trendel.	6

HAEMORRHAGE (Appreciable) 27
Blood given
Other fluids given

ANAESTHETIC AGENTS 32
(i) *a.* Thiopentone 1
b. Cyclopropane 2
c. Pethidine 3

(ii) *a.* Nitrous Oxide 1 33
b. Ether 2
c. Trilene 3
d. Chloroform 4

(iii) *a.* Vinesthine 1 34
b. Ethyl Chloride 2

RELAXANTS Tubarine 1 35
Flaxedil 2
D.M.E. 3
Scoline 4

REVERSING AGENTS Atropine } 1 36
Prostigmine }
None 0

LOCAL ANALGESICS Type 1 37
Agent 2

RADIOTHERAPY Yes 1 38
No 0

LENGTH OF OPERATION 39
Under 1 hour 1
Over 1 hour 2

FORECAST OF VOMITING 40
Correct 1
Incorrect 2

III

PREVIOUS ANAESTHETIC HISTORY 28
None 0
With vomiting 1
Without vomiting 3

NAUSEA 29

Nil	0	Moderate	2
Slight	1	Severe	3

SUBJECTIVE VOMITING 30

Nil	0	Moderate	2
Slight	1	Severe	3

OBJECTIVE VOMITING 31

Nil	0	Moderate	2
Slight	1	Severe	3

DURATION OF VOMITING (hours post op) 41 42
Started .....
Ceased .....

NUMBER OF VOMITS 43

DID it follow food 1 44
drink 2
Neither of above 3

POST OPERATIVE ANALGESICS 46
Before vomiting started 1
After 2

FIG. 1

being the same as the observed vomiting, the latter being considered the only reliable index in these cases.

RESULTS

There were 2,528 cases in the survey of whom 1,702 (67.5 per cent) formed the control group, 490 (19.4 per cent) lay in the group receiving promethazine and 111 (4.4 per cent) received chlorpromazine (table I). The 61 cases who were vomiting before operation and the 156 cases with Ryle's tubes were analyzed separately. There were 8 cases who received both phenothiazine derivatives. It will be seen from table I that the subjective and objective vomiting rates are so similar that in all other tables only objective vomiting is recorded.

The various vomiting rates are markedly decreased when either of the phenothiazine derivatives are used, but the difference between the two is small. Those cases who were vomiting before operation showed, not unexpectedly, a higher incidence of postoperative vomiting. The cases with Ryle's tubes show lower rates of vomiting than the mean, but about the same incidence of nausea.

Premedication.

Many different combinations of drugs were used as premedicants, some too rarely to show any statistically significant results, but the combination of pethidine and scopolamine was used most frequently (table II), 1,542 cases (61 per cent) received these drugs with or without promethazine or chlorpromazine. In the control group, and in the other two groups, the cases who received pethidine showed a lower incidence of vomiting than those having papaveretum or morphine. Barbiturates were administered largely to children, therefore the vomiting rates are relatively high (see table VII).

The lowest vomiting rates were found when atropine or hyoscine was used alone, though this may be due to the minor procedures for which such drugs only were prescribed.

It is apparent from table I that both chlorpromazine and promethazine are approximately equally effective in reducing postoperative vomiting. The drug most commonly favoured in the literature at present is chlorpromazine, which has several side effects including delayed recovery of consciousness, hypotension, dizziness, vasodilatation, occasional pre-operative restlessness, and pain on intramuscular injection (Dripps et al., 1955) which make it unsuitable, in our opinion, for routine pre-operative medication, although it does undoubtedly reduce the incidence of postoperative vomiting (Albert and Coakley, 1954; Burn, 1954; Becker, 1954; Beard, 1954; Laborit and Hugenard, 1954; Vandewater and Gordon, 1955; Dripps, 1955). The effect of a given dose is also very variable.

We found promethazine preferable to chlorpromazine as the undesirable side effects of the latter were to a great extent avoided without any loss of anti-emetic action. The side effects of promethazine appear to be occasional mild dizziness and a cerebral depressant action, which is additive to the other anaesthetic agents and premedicants used,

TABLE II

Analysis of the Control Group by premedicant drug	Objective vomiting		
	Cases	Slight	Severe
		%	%
Morphine	38	29	13.2
Papaveretum	438	27	10.5
Pethidine	1094	21.8	6.6
Barbiturates *	84	31	11.9
Atropine or hyoscine only	45	20	4.6
Others	3		
Totals	1702	23.7	7.9

Analysis of Test Group by premedicant drug	Objective vomiting		
	Cases	Slight	Severe
		%	%
Pethidine and promethazine or chlorpromazine	448	16.1	2
Barbiturates and promethazine or chlorpromazine	35	17.6	2.8
	483	16	2

* These cases were almost entirely children.

and does mean that decreased dosage of other drugs is generally indicated. For this reason both chlorpromazine and promethazine should be used sparingly when very rapid recovery is desired or in very old and frail patients. Patients came to the theatre well sedated but rousable and there was no restlessness. Recovery of essential reflexes was not delayed in the great majority of cases, the antispasmodic action of the drug (Dinnick, 1955) depressed laryngeal reflexes as well as inhibiting bronchospasm. Postoperative recovery was uneventful.

It is possible that the substitution of the morphine derivatives by barbiturates would further reduce vomiting, but only in our opinion at the expense of having less satisfactory sedation.

Patients premedicated with a barbiturate, scopolamine and promethazine were euphoric and unworried, but were often restless and needed more thiopentone if this was followed by nitrous oxide and oxygen only.

If on the other hand, anaesthesia was maintained by a powerful agent such as cyclopropane, anaesthesia was satisfactory and with this technique, in adults, a low incidence of vomiting was recorded. For minor procedures in older patients a combination of promethazine and scopolamine alone proved very satisfactory.

However, for routine use our choice of premedication to reduce postoperative vomiting and retain satisfactory sedation is promethazine 50 mg, pethidine 50 mg, scopolamine 0.2 mg by injection, but we believe there is scope for the use of other premedicants depending on the age and sex of the patient and the type of anaesthetic to be administered.

ANAESTHETIC AGENTS

Thiopentone was used for induction in the great majority of cases. Of the agents used for maintenance of anaesthesia, nitrous oxide and oxygen was associated with the lowest vomiting rate (18 per cent), but the addition of intravenous pethidine increased the vomiting rate to 30 per cent. This is partially due to the fact that the latter cases probably underwent more major procedures, but nevertheless we believe the difference to be significant, for when pethidine was added to nitrous oxide, oxygen and trichloroethylene anaesthesia, the vomiting rate rose from 26 per cent to 46 per cent.

Of the other agents used, cyclopropane (24 per cent) caused less vomiting than trichloroethylene (26 per cent) or ether (33 per cent). This agrees with the findings of Waters (1936), Davies (1941) and Dent et al. (1955) who all agree that ether is

TABLE III

Incidence of vomiting associated with varying anaesthetic agents.

Anaesthetic agents	Cases	Objective vomiting		Total vomiting	
		Slight	Severe		
		%	%		
Thiopentone–N_2O–O_2 ± relaxant	364	15	3.3	18.3	
Thiopentone–N_2O–O_2 ± relaxant and pethidine	382	21.8	7.7	29.5	
Thiopentone–cyclopropane ± relaxants	378	18.3	5.6	23.9	
Thiopentone–N_2O–O_2–ether ± relaxants	512	25.4	8	33.4	
Thiopentone–N_2O–O_2–trichloroethylene ± relaxants	417	23	3.4	26.1	=30.5
Thiopentone–N_2O–O_2–trichloroethylene + pethidine	82	28	18.3	46.3	
Others	393	21.6	9.9	31.5	
Mean	2528				

TABLE IV

Agent	Waters (1936)	Davies (1941)	Dent et al. (1955)	Burtles and Peckett (1956)
	%	%	%	%
Nitrous oxide	23	27	20	18
Ether	56.5	40	38.5	33
Cyclopropane	39	—	34.6	24

TABLE V

Incidence of vomiting associated with varying relaxants.

Relaxants	Cases	Objective vomiting		Total vomiting
		Slight	Severe	
		%	%	%
Suxamethonium	757	25.2	8.1	33.6
Tubocurarine	222	24.3	9	33.3
Gallamine	193	21.8	5.7	27.5
Tubocurarine and suxamethonium	164	18.9	4.9	23.8
Dimethyl tubocurarine	50	24	8	32
Mean	1386	24	7.5	31.5
No relaxants	1142	18	5.8	23.8

associated with the highest vomiting rates and nitrous oxide-oxygen with the lowest.

Difficult inductions with spasm, swallowing, and cyanosis occurred only rarely, but when they did there was surprisingly little change in the incidence of vomiting.

Our figures conform with the progressive improvement in postoperative vomiting that has occurred in the last twenty years. It must be pointed out that of these percentages shown the great majority of our cases had only the mildest vomiting. Severe vomiting as defined by us occurred in only 2.8 per cent of cases.

Relaxants and Intubation.

1,386 cases (55 per cent) received relaxants and 1,289 cases (51 per cent) were intubated. The vomiting rates in both groups are higher than the general mean; 31.5 per cent of these receiving relaxants vomited, against 24 per cent of those who were not given such drugs.

Probably relaxants themselves influence sickness very little and the above difference can be explained by the more severe and prolonged operations requiring relaxants.

Those cases receiving both tubocurarine and suxamethonium had the lowest vomiting rates (24 per cent). This may be because such cases were maintained on the nontoxic nitrous oxide-oxygen mixture; the suxamethonium group, which had the highest vomiting rate (34 per cent) were generally maintained on ether, trichloroethylene or cyclopropane.

Endotracheal Intubation.

Table VI shows that the various forms of endotracheal intubation are associated with different rates of vomiting. The difference in vomiting rates between "Blind Nasal" and "Visual Nasal" (using a laryngoscope and/or forceps) is not understood. But it is unlikely that the endotracheal tube or reversing agents are important factors in influencing the incidence of vomiting.

TABLE VI

Incidence of vomiting associated with varying methods of intubation.

	Cases	Objective vomiting		Total vomiting
		Slight	Severe	
		%	%	%
Oral	629	26.9	7.5	34.4
Cuffed oral	369	20.8	6.2	27
Visual nasal	224	21.5	7.2	28.7
Blind nasal	67	15	3	18
Mean	1289	23.5	6.8	30

Length of Operation.

It will be seen from table VII that operations were divided into those taking less than one hour and those taking more. The longer operations had an almost 50 per cent increase in vomiting, particularly in the severe group.

Age and Sex.

It will be seen from table VIII that the incidence of vomiting is higher in females than in males at all ages, particularly after the first two decades and that vomiting steadily decreases in both sexes with increasing age. Vomiting is twice as common in women as in men over the age of 20. About 42 per cent of our cases were males and 60 per cent of each group were over 40 years of age.

Posture during operation.

Table IX shows that 2,574 positions were recorded on the record forms, which means that

TABLE VII

Incidence of vomiting as related to length of operation.

	Cases	Objective vomiting		Total
		Slight	Severe	
		%	%	%
Under 1 hour	1656	19.4	5	24.4
Over 1 hour	788	26.5	9.3	35.8

TABLE VIII

Incidence of vomiting as related to age and sex.

Age and sex	Cases	Objective vomiting		Total
		Slight	Severe	
Males		%	%	%
0 – 9	81	42	10	52
10 – 19	56	35.8	9	44.8
20 – 39	274	15.3	3.7	19
Over 40	628	11.6	2.2	13.8
	1039			
Females				
0 – 9	51	31.4	25.5	56.9
10 – 19	71	33.8	14.1	47.9
20 – 39	433	26	8.5	34.5
Over 40	869	24.6	3.2	27.8
	1424			

TABLE IX

Incidence of vomiting as related to posture.

Position	No. of Cases	Objective vomiting		Total
		Slight	Severe	
		%	%	%
Supine	1534	20.6	6.7	27.3
Lithotomy	500	18	3.8	21.8
Trendelenburg	159	25.8	6.3	32.1
Reversed Trendelenburg	147	33.4	9.5	42.9
Lateral	145	17.9	6.9	24.8
Prone	89	21.4	10.1	31.5
Means	2574	21	6.9	

46 cases were operated on in two postures (e.g. cystoscopy proceeding to prostatectomy). 61 per cent of cases were operated on in the supine position and their overall vomiting rate was 27 per cent. The reversed Trendelenburg and Trendelenburg positions were associated with high vomiting rates, probably because a large proportion of operations in these positions are carried out on the female, for example gynaecological abdominal surgery, varicose vein surgery, thyroidectomies and mastectomies. Collins (1952) suggests that sudden movements such as rough handling during transportation postoperatively may cause vomiting.

20 per cent of cases were operated on in the lithotomy position which was associated with the lowest vomiting rate (22 per cent).

Site of Operation.

From time to time it has been suggested that the site of operation bears an important relationship to the rate of vomiting. Fenestrations and thorocoplasties under local anaesthesia (Beard, 1954) have been associated with considerable vomiting. Davies (1941) gives a vomiting rate of 67 per cent for the operation of dilatation of the cervix and curettage. He also says that the popular idea that operations in the mouth have a high vomiting rate because of swallowed blood is not correct. His rate was 49 per cent (control group 44 per cent).

From table X it will be seen that in our series of cases the operation of fenestration had a vomiting rate of 75 per cent, by far the highest incidence of vomiting recorded. Dilatation and curettage had a vomiting rate of 24 per cent, below average for the whole series, but comparatively high for a minor procedure. This may be explained in that it is an operation confined to the female sex, but the insertion of radium ovoids, a somewhat similar procedure, carries a rate of only 17 per cent. The average age of these patients however is notably higher.

Operations in the mouth in adults were not associated with high rates of vomiting: 114 dental extractions carried out on in-patients with endotracheal nitrous oxide-oxygen-ether had a vomiting rate of 14 per cent and only 3 per cent cases had other than very mild sickness. Whereas tonsillectomy operations in children (122 cases), again under ether anaesthesia, had a vomiting rate of 28 per cent.

Here again age is probably an important factor; also much deeper ether anaesthesia is required for tonsillectomies in children carried out without intubation than in adult dental extractions with light endotracheal ether anaesthesia.

The overall percentage sickness in abdominal and extra-abdominal procedures was very similar (25 and 28 per cent). Thoracic operations were associated with a slightly lower figure (21 per

TABLE X

The incidence of vomiting with varying operations.

Site of operation	No. of cases	Slight sickness	Moderate or severe sickness	Total sickness
		%	%	%
In-patient dental extractions	114	11.4	3	14
Insertion of radium to cervix	73	12	4.5	17
Genito-urinary	233	13	7	20
Bronchoscopy / Oesophagoscopy	43	14	7	21
Thorax	52	17	4	21
Neurosurgery	42	12	9	21
Dilatation and curettage	74	22	1.5	24
Abdominal	424	18.4	7	25
Extra-abdominal	1030	21.3	6.8	28
Tonsils and adenoids	122	15.7	12.4	28
Other E.N.T. operations	190	21.6	6.9	28
Thyroidectomies	31	23	10	33
Eye operations	80	25	11.5	36
Fenestrations	20	35	40	75
Totals	2528	18.7	9.3	28

cent), possibly due to the anaesthesia generally being nitrous oxide, oxygen and d-tubocurarine, whereas extra-abdominal procedures were often carried out under ether, trichloroethylene or cyclopropane. Operations on the eyes, in our series, were associated with a relatively high incidence of vomiting.

Generally speaking short procedures such as dental extractions, the insertion of radium, cystoscopies, bronchoscopies, oesophagoscopies and dilatation and curettage of the cervix and uterus were associated with lower vomiting figures than longer and more major procedures, and it appears that apart from operations such as fenestrations, the site of operation is not so important as its duration and severity in influencing the incidence of postoperative vomiting.

DISCUSSION

We have stressed the importance of a number of factors influencing the incidence of postoperative vomiting, particularly the age and sex of the patient, the length of operation, the premedication and anaesthetic agents used and, to a lesser extent, the posture of the patient and the site of operation.

There are many other factors that we tried to assess as can be seen from figure 1. Pre-operative vomiting was not common, but occurred both before and after premedication, and these patients tended to be more sick postoperatively. There is no doubt in our minds that postoperative morphine derivatives increase postoperative vomiting and pethidine and methadone have advantages over morphine in this respect. Gross anoxia, as can be occasionally seen from badly administered nitrous oxide in the casualty departments, undoubtedly causes vomiting, but mild attacks of spasm and cyanosis as seen infrequently in this series did not apparently increase vomiting.

Ryle's tubes tend to decrease vomiting but have little effect on nausea and retching.

The previous anaesthetic history is important in forecasting whether a patient will be sick. Even after antihistamines patients who admit to always being very sick after anaesthesia may still vomit, but the severity and duration are usually drastically reduced and with care in avoiding as many predisposing factors as possible and repeated injections of 50 mg of promethazine vomiting can in the majority of cases be controlled.

A history of travel sickness or easily induced vomiting similarly should encourage the anaesthetist to administer pre-operative and possibly post-operative promethazine.

If care is taken in assessing the patient an accurate estimate of the possibilities of vomiting can be made but there will always in our experience be about 10 per cent of people who will be unexpectedly sick.

A major proportion of the vomiting occurred when the patients recovered consciousness, complained of thirst, and had a large drink of water or fruit juice; or in the morning following operation they vomited up their breakfast. It is possible, by cutting down oral fluids immediately post-operatively, vomiting could again be reduced.

Most of the radiotherapy cases in our series were short procedures and the patients elderly, so vomiting rates were not high. Sickness associated with radiotherapy did not usually develop in the first 36 hours.

Local analgesia was always associated with general anaesthesia in our series and did not obviously influence the vomiting rates.

SUMMARY

2,528 cases have been followed up to assess the current incidence of postoperative vomiting in this hospital.

It is shown that promethazine and chlorpromazine reduce this rate by 50 per cent. Reasons are given why promethazine was preferred.

The vomiting rates associated with differing premedicant and anaesthetic drugs are analyzed and the effects of age, sex and duration of operation are shown to be important.

ACKNOWLEDGMENTS

We should like to thank all the staff of the Middlesex Hospital who so patiently co-operated with us in obtaining the information for this paper, particularly the Anaesthetic Consultant Staff, the other members of the Anaesthetic Department and all the Ward Sisters and Nursing Staff for their help. We are indebted to Mr. Cowan of the Records Department for his great help with the statistical analysis.

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CORRESPONDENCE

POTASSIUM DEPLETION AND THE CENTRAL ACTION OF CURARE

Sir,—Dr. Patrick A. Foster in his letter (*Brit. J. Anaesth.* (1957), **29**, 47) tells us that case No. 7 in his article "Potassium Depletion and the Central Action of Curare" (*Brit. J. Anaesth.* (1956), **28**, 488) was in "good condition"; I confess that this surprises me in view of the electrolyte state 12 hours later. That there was then a low potassium serum level and that prolonged coma occurred are two facts, but there is not necessarily a direct connexion between them.

On January 24, 1957, I anaesthetized a woman of 49, weighing only 5½ stones (this fact should be taken into account when considering the doses detailed below). She was suffering from some nutritional disorder, and underwent a diagnostic laparotomy. She had oedema of the legs and sacral region, and her serum potassium level was 3.1 m.equiv./l. (cf. Dr. Foster's case No. 7, in which it was 3.3 m.equiv./l.). After premedication with morphine 10 mg and atropine 0.45 mg two hours before operation, she was given a "sleep dose" of thiopentone (50 mg), induction was completed with nitrous oxide and ether, and she was intubated (5 minutes). Thereafter, anaesthesia was continued with nitrous oxide. Shortly after the incision (12 minutes) she was given dTC 5 mg, with subsequent doses up to a total of 13 mg. Relaxation was profound and respiration ceased: artificial respiration was performed by manual compression of the bag of a Waters canister, the the flowrate of N_2O being 1½ l./min, and of O_2 1 l./min. Breathing was restarted by administering CO_2 as soon as the rectus sheath was closed (61 minutes), and became adequate on administering neostigmine 1 mg (62 minutes); atropine 0.65 mg had been given (56 minutes). Recovery has been uneventful.

This case seems to show that Dr. Foster's facts are not necessarily directly related, but, in this case, as in all, the situation is so complicated that great care ought to be taken in drawing conclusions.

As for the safety with which large doses of neostigmine can be given, perhaps I may be forgiven for pointing out that the three patients given 15, 20 and 15 mg respectively all died.

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Brit. J. Anaesth. (1957), **29**, 124

ARTIFICIAL HIBERNATION FOR ECLAMPSIA

A Case Report

BY

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DESPITE the highest standard of antenatal care, sporadic cases of eclampsia still occur, and their treatment is a major obstetric problem. In recent years the principles of treatment have been established: control of the fits for 24 hours followed by termination of the pregnancy. As a method of controlling eclamptic fits, we believed that artificial "hibernation" with phenothiazine derivatives might have advantages over more usual sedatives for the following reasons:

(1) These drugs produce prolonged and profound sedation.
(2) They produce hypotension.
(3) Vasodilatation, through their action on the autonomic nervous system may minimize renal cortical damage.
(4) These drugs need not be used to the exclusion of other sedatives, but by virtue of their potentiating effect, the effective dose of other sedatives may be reduced.

Aoustin (1953) described the first case of eclampsia treated by artificial hibernation and Baccaglini (1953), Centaro (1953), Röttger (1953) and Rouchy and Creze (1953) also described the treatment of this condition with various phenothiazine derivatives.

Araujo (1953) reported a group of 59 eclamptic patients treated with chlorpromazine and promethazine, with a maternal mortality of 6.7 per cent. Mitra and Das Gupta (1955) described 46 cases similarly treated with one death and it is significant that 18 of these cases had more than ten fits after treatment had started. Further cases were reported by Cliche and Fortnin (1955) and by O'Keefe, Shanahan and Quane (1955). Hudson and Siew (1956) reported 30 cases with one maternal death and a foetal death mortality of 43.3 per cent; in 11 of these cases fits occurred after treatment.

CASE REPORT

A primigravida of 21 years, who was expecting her baby on February 16, 1956, was seen at monthly intervals during the first six months of her pregnancy, when her blood pressure varied between 120/80 mm Hg and 110/70 mm Hg.

On November 18, 1955 (at the 27th week of her pregnancy), the patient noticed some swelling of her ankles and three days later there was puffiness of her face. On November 24 at 6 a.m., and whilst in bed at home, an eclamptic fit occurred, and this was followed thirty minutes later by a second fit when morphine sulphate 15 mg was given subcutaneously by the patient's own doctor. On arrival at hospital at 7.10 a.m., a further eclamptic fit lasting two minutes occurred. On examination the patient was in coma with stertorous respiration; there was gross oedema of the face, hands and ankles, and the blood pressure was 170/120 mm Hg. A catheter was passed and the urine obtained boiled solid with albumin. The ocular fundi were of normal appearance.

At 7.30 a.m., 20 ml of a mixture containing chlorpromazine 50 mg, promethazine 50 mg, and pethidine 50 mg in physiological saline (hereafter called "the mixture") was given intravenously and this was followed by an immediate fall in blood pressure to 120/90 mm Hg.

At 9.30 a.m., an eclamptic fit occurred as a result of minimal stimulation and a further 15 ml of the mixture was given.

At 11 a.m. the blood pressure started to rise steadily and 20 minutes later an eclamptic fit occurred without any precipitating factor; a further 20 ml of the mixture was given and the blood pressure fell from 150/120 mm Hg to 130/90 mm Hg after 10 minutes.

At 1.15 p.m. a further 20 ml of the mixture was given and its hypotensive effect was delayed for 20 minutes. During this time, at 1.25 p.m., the patient was turned and an eclamptic fit occurred.

At this stage the patient had been "hibernated" for 7 hours and had received 75 ml of the mixture in four doses, and during this time three eclamptic fits occurred. It was concluded that adequate control of the fits was not being achieved by the mixture, and it was decided to abandon the treatment of the patient by "hibernation" alone. An initial dose of thiopentone 0.25 g was followed an hour later by sodium phenobarbitone 3 grains (180 mg). During the next 20 hours sedation was maintained by sodium phenobarbitone and paraldehyde primarily, though three injections of 20 ml of the mixture were given during this time: no further fits occurred.

Twenty-eight hours after admission abdominal

hysterotomy was performed. After premedication with hyoscine 0.45 mg, 20 ml of the mixture was given by intravenous injection before removal to the operating theatre. The anaesthetic technique was a standard thiopentone, nitrous oxide, oxygen, relaxant sequence with orotracheal intubation and controlled respiration. A nonviable foetus weighing 1 pound 10 ounces (0.28 kg) was delivered by a lower segment operation. The patient's condition was good when she left the theatre (blood pressure 110/85 mm Hg; pulse rate 92 per minute; respiratory rate 24 per minute).

Sedation was continued with intermittent intramuscular paraldehyde and consciousness was regained 18 hours after operation. Forty-eight ounces of urine was passed in the 28 hours following the first fit, i.e. prior to hysterotomy, but in the following 12 hours only 3 ounces of dark, blood-stained urine were secreted and a splanchnic block was performed using the posterior approach (Kappis, 1919). The blood pressure fell at once from 125/110 mm Hg to 100/80 mm Hg, but diuresis did not occur until 14 hours later when 9 ounces (256 ml) of urine was obtained from the indwelling catheter. From this time the patient made a slow but uninterrupted recovery.

DISCUSSION

The pre-operative treatment of this patient lasted for 28 hours and was in three phases (fig. 1):

Phase 1, from 7.30 a.m. until 2.30 p.m. on November 24 (7 hours).

Sedation during this period was with a mixture containing chlorpromazine, promethazine and pethidine previously described. A total dose of 75 ml of this mixture was given by intravenous injection in four doses at approximately 2-hourly intervals. Initially the mean blood pressure fell from 150 mm Hg to 105 mm Hg and this hypo-

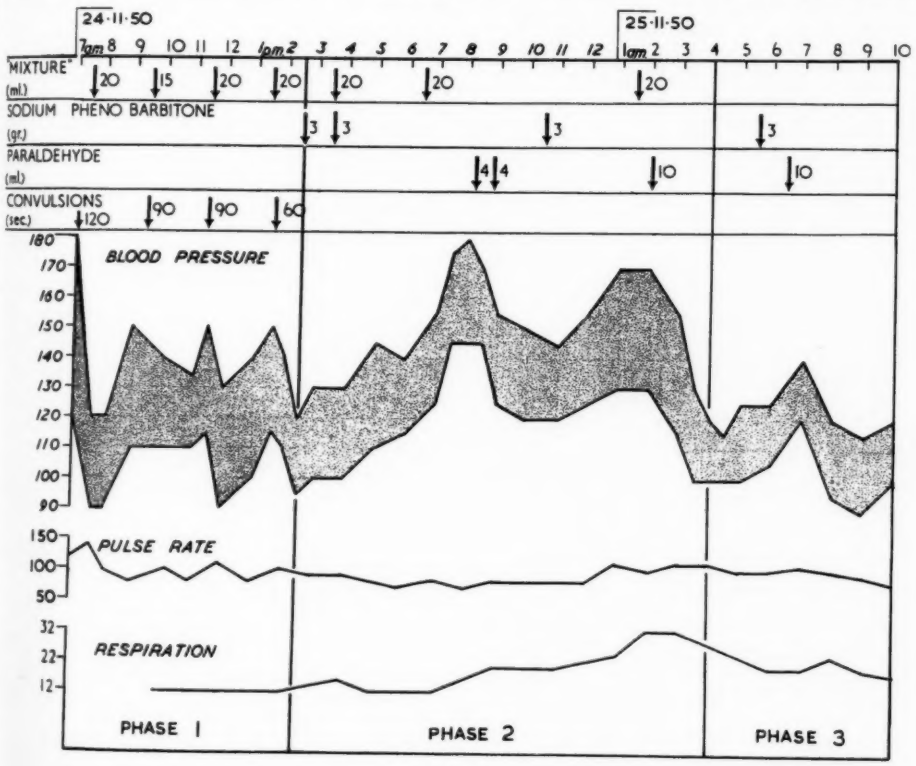

FIG. 1

Relating blood pressure, pulse rate, respiratory rate and occurrence of eclamptic fits with treatment by the "mixture" (chlorpromazine 50 mg, promethazine 50 mg, pethidine 50 mg), sodium phenobarbitone and paraldehyde, and showing the division of treatment into the three phases described in the text.

tensive effect was maintained throughout phase 1, the average mean pressure being 117 mm Hg. It was noted, however, that the immediate fall in pressure following successive doses of the mixture progressively diminished. The average pulse rate was 90 per minute and the respiration rate 12 per minute.

"Hibernation" failed to control the eclamptic fits and three convulsions occurred after treatment commenced. As described by Hudson and Siew (1956), these fits were modified and of a minor degree, the longest lasting 1½ minutes.

Phase 2, from 2.30 p.m. November 24, to 4 a.m. November 25 (13½ hours).

During this period a total dose of 9 grains (540 mg) of sodium phenobarbitone and 18 ml of paraldehyde and, in addition, three intravenous injections, each of 20 ml, of the chlorpromazine-promethazine-pethidine mixture, was given. The mean blood pressure rose steadily from 117 mm Hg to 160 mm Hg during the first 5½ hours of this phase and the average mean pressure for the next 6 hours was 140 mm Hg; a fall in pressure to a mean level of 110 mm Hg then occurred.

Despite the rise of the blood pressure during phase 2, no further eclamptic fits occurred. The respiration rate gradually increased to 20 per minute and the pulse rate was steady at 80 per minute.

Phase 3, from 4 a.m. until 10 a.m. on November 25 (6 hours).

Sedation during this phase was exclusively with sodium phenobarbitone 3 grains (180 mg) and paraldehyde 10 ml. The mean blood pressure averaged 110 mm Hg, the pulse rate was 100 per minute and the respiration rate 20 per minute. During this phase no eclamptic fits occurred.

CONCLUSIONS

The chlorpromazine-promethazine-pethidine mixture effectively lowered the blood pressure during the first seven hours of treatment, but successive doses of the mixture were progressively less effective in this respect. Artificial hibernation alone was ineffective in controlling eclamptic fits, but when barbiturates and paraldehyde were added, no further convulsions occurred.

Dobkin, Gilbert and Lamoureux (1954) have shown that chlorpromazine is effective in preventing induced convulsions in the frog and the rabbit and that it produces a normal sleep electroencephalogram pattern in man. These observations suggest that chlorpromazine has a poor anticonvulsant action and barbiturates are required in addition when these drugs are used in the treatment of eclampsia.

We think it is significant that the administration of phenothiazine derivatives alone failed to control eclamptic fits in this case, and it would appear that the role of these drugs should be to potentiate rather than to replace established methods of sedation.

ACKNOWLEDGMENTS

We wish to thank Miss Josephine Barnes, D.M., F.R.C.S., F.R.C.O.G., for permission to publish this case report.

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Brit. J. Anaesth. (1957), **29**, 127

IRREVERSIBLE CURARIZATION

BY

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FOUR cases of irreversible curarization are detailed below. They occurred during the last four years. Cases 1 and 4 were anaesthetized by the writer, and cases 2 and 3 by two colleagues.

CASE 1

Female aged 69 years. Very obese. Large incisional hernia developing for twenty years since hysterectomy. Three months colicky pain.

Three days before admission started to vomit. Vomit became brown, very foul smelling and projectile in character.

Past history. Chronic bronchitis. Breathless only on exertion.

On examination. Mucous membranes pale, tongue dry.

Abdomen.

Large irreducible hernia.

Chest.

Lungs poor expansion, poor air entry. Scattered râles and rhonchi over whole chest.

Cardiovascular system.

Blood pressure 180/110 mg Hg. Apex beat in fifth space. No sign of congestive heart failure.

Operation. Three hours after admission hernia was reduced, no gangrene of bowel. Hernia repaired.

Anaesthetic.

Pre-operative preparation. Aspiration of stomach with large bore tube and erection of intravenous saline drip.

Premedication. Papaveretum 10 mg: hyoscine 0.15 mg.

Anaesthesia was induced with 150 mg thiopentone and 25 mg of d-tubocurarine; intubated with No. 10 cuffed Magill's endotracheal tube. Anaesthesia maintained with oxygen (25 per cent) and nitrous oxide (75 per cent). Relaxation was good. Controlled respiration was used from the start and continued until the repair was complete. The soda lime canister was removed from the circuit and CO_2 allowed to accumulate. By the end of the operation a small, regular, jerking diaphragmatic movement started. The movement was insufficient to keep the patient fully oxygenated even on 100 per cent oxygen.

She was then given 5 per cent CO_2 for five minutes but with no change in respiration. The patient was then given 0.9 mg of atropine followed by 2.5 mg neostigmine. No change occurred in the patient's respirations.

Blood pressure was maintained between 140/80 and 160/90 mm Hg. Respiration aided by 50/50 mixture of nitrous oxide and oxygen. After ten minutes nikethamide 5 ml given—no change in respiration. After further wait, nikethamide 5 ml repeated—no change in respiration.

Next the patient was hyperventilated for ten minutes with CO_2 absorption to exclude the possibility of CO_2 causing respiratory depression—no change in respiration.

After two hours respiration was still the same and atropine 0.9 mg and neostigmine 2.5 mg was repeated but with no effect.

The endotracheal tube was removed in case respiration was being reflexly inhibited but this had no effect and so the tube was replaced.

Further neostigmine was given to a total of 12.5 mg.

Five hours after the start of the anaesthetic the blood pressure started to fall and dropped rapidly to 70/40 mm Hg.

A noradrenaline drip was started but the systolic blood pressure would not rise above 90 mm Hg. Two hours later the blood pressure dropped swiftly and the patient died.

During this period of resuscitation the controlled respiration was withheld from time to time and the characteristic small jerky movements of the diaphragm resumed. They were never strong enough to maintain full oxygenation even on 100 per cent oxygen.

Postmortem examination.

Lungs. Extreme oedema of all lobes—extensive old adhesion on left.

Heart. Moderate hypertrophy of left ventricle. Coronary arteries and heart muscle normal.

Liver. Large, soft and fatty.

NOTE

The patient's condition at the end of the operation was excellent except for the depressed respiration (accepted as normal in such a case). Pulse was of good volume, blood pressure 150/80 mm Hg, pulse rate 84. Circulatory failure did not occur until four hours later and was clearly secondary to prolonged controlled respiration. Oedema of the lungs was probably terminal.

CASE 2

Female aged 68 years presented with strangulated umbilical hernia of four days duration.

On examination. Very obese woman. Lungs clear.

Cardiovascular system. Pulse 104. Blood pressure 130/70. Heart sounds normal.

Anaesthetic.

Pre-operative preparation. Similar to case 1.

Premedication. Morphia 10 mg: atropine 0.6 mg.

Induction. Thiopentone 300 mg: d-tubocurarine 15 mg. Cuffed tube. Controlled respiration throughout operation.

At the end of the operation respirations were of same jerky inadequate nature as in case 1. The patient was treated with atropine 0.6 mg and neostigmine 2 mg. and nikethamide 5 ml to no avail.

Circulatory failure and then death one hour after end of operation.

Postmortem examination.

Heart. Valves healthy. Left ventricle normal. Right ventricle dilated and hypertrophied. Coronary arteries showed confluent fatty atheroma but were widely patent.

Lungs. Marked oedema of upper lobes. Walls of of small bronchi slightly thickened.

Liver. Pale and greasy.

Kidney. Mild pyelitis, otherwise healthy.

NOTE

Same sequence as case 1. Circulatory failure quicker in onset and preceding death.

CASE 3

Female aged 75 years admitted with history of vomiting for three days, becoming steadily worse and at the time of admission consisting of projectile vomiting of foul smelling brown material.

On examination. Abdomen distended. Left strangulated femoral hernia.

Cardiovascular system.

Pulse rate 100/min regular. Heart, N.A.D. Blood pressure 120/90 mm Hg.

Respiratory system.

N.A.D.

The patient was given an enema for diagnostic purposes and this caused her condition to deteriorate rapidly. Blood pressure falling to 80/? mm Hg.

She was then given intravenous fluids and her blood pressure rose rapidly to previous level. She received 2 litres of normal saline and 1 litre of 5 per cent glucose in saline before operation. A gastric tube was passed andleft in situ.

Blood chemistry. Na 130 m.equiv; K sample too haemolysed for estimation; Cl 92.5 m.equiv; urea N 46 mg per cent; urea 98.5 mg per cent.

Operation. 12.35 p.m. Richter's hernia. Gut viable.

Anaesthesia.

Premedication. Papaveratum 10 mg: atropine 0.6 mg.

12.20 p.m. Induction thiopentone 200 mg and suxamethonium 40 mg. Intubated with cuffed tube. Blood pressure 120/90 mm Hg.

12.35 p.m. Spontaneous respiration started. d-Tubocurarine 15 mg given.

12.37 p.m. Respiration ceased. Controlled respiration started with N_2O and O_2 2:1 mixture using a Waters canister.

1.0 p.m. Operation finished. CO_2 given. Respiration started but could only be described as diaphragmatic flutter and not of sufficient amplitude to maintain oxygenation.

1.10 p.m. Atropine 0.6 mg given intravenously.

1.15 p.m. Neostigmine 2.5 mg I.V. No response.

1.20 p.m. Nikethamide 3 ml I.V. No response.

1.30 p.m. Atropine 0.6 mg I.V.

1.35 p.m. Neostigmine 0.5 mg I.V.

1.40 p.m. Respirations further diminished.

1.50 p.m. Respirations ceased.

2.15 p.m. Blood pressure started to fall. Patient became cyanosed despite 100 per cent O_2. 15 mg methylamphetamine sulphate given I.V. Blood transfusion started.

3.15 p.m. Nikethamide 5 ml given. No effect on respiration or circulation.

4.0 p.m. Died from circulatory failure.

Postmortem examination.

Lungs. Oedematous, believed to be terminal manifestation.

Heart. Muscle pale and soft. No lesions seen in coronaries or valves.

Liver. Advanced cloudy swelling.

Kidney. Slightly granular appearance.

NOTE

This was the only case with blood chemistry figures available. They were as expected. Some correction of Na, Cl, and urea may have taken place from infusion of saline pre-operatively as the sample was taken about six hours before operation. Respirations in this case seemed to become less after neostigmine.

CASE 4

Female aged 81 years admitted with history of abdominal pain and vomiting for three days.

On examination. Tense, strangulated right femoral hernia. History of bronchitis and emphysema, slightly breathless when seen pre-operatively. Blood pressure 160/90 mm Hg. Colour good, pulse rate 90/min. regular. No cardiac murmurs.

Anaesthetic.

Routine pre-operative preparation. Gastric tube inserted and intravenous saline commenced.

Premedication. Atropine 0.45 mg: pethidine 50 mg induced with 100 mg thiopentone, 10 mg d-tubocurarine. Intubated with ease, relaxation good. Respirations reduced to diaphragmatic flutter. Controlled respiration instituted with 70 per cent N_2O and 30 per cent O_2. Patient maintained on this mixture during operation. Colour excellent, pulse regular 85/min. Blood pressure varied between 140 and 160 mm Hg systolic.

At the end of the operation, taking one hour, during which the hernia was successfully reduced, the patient's condition was exactly similar to that seen in the previous three cases. There was still this diaphragmatic flutter but insufficient movement to oxygenate the patient. CO_2 inhalation failed to stimulate respiration.

Atropine 0.6 mg was given intravenously followed by 1 mg neostigmine. Then a further 1 mg neostigmine with no change in respiration.

The patient was then hyperventilated with CO_2 absorption to eliminate the possibility of CO_2 apnoea. This caused abolition of small respiratory movement present. This movement returned with further administration of CO_2. Nikethamide 5 ml intravenously had no effect.

Seven and a half hours after induction the blood pressure started to fall and she went into peripheral circulatory failure and despite methylamphetamine sulphate, noradrenaline and blood she died 45 minutes later—eight and a quarter hours after induction.

Postmortem examination.
Lungs. Chronic vesicular emphysema.
Liver. Fatty.
Heart. Normal.

DISCUSSION

A summary of these four cases will be found in tables I and II.

All the patients were poor risk cases with intestinal obstruction of three to four days duration with severe vomiting. The blood chemistry in all cases must have been disturbed although estimations were only made in case 3. They had taken no food for two to three days before admission so that they were in a state of starvation. There was toxic damage to the liver in all cases. Although in no case was the condition of the heart and lungs normal, there was not sufficient disease to account for sudden death. At the time it was thought that toxaemia contributed to the sudden death of these patients.

Death from toxaemia is usually characterized by primary circulatory failure with falling blood pressure and rapid pulse. These patients all had a primary failure of respiration and although circulatory failure was present at the end it was a terminal event. Respiration was adequate in all cases until d-tubocurarine was given.

This had a prolonged paralytic effect uninfluenced by the subsequent administration of neostigmine. They presented a definite syndrome characterized by:

(1) A normal dose of d-tubocurarine caused a normal degree of paralysis; some respiratory movement was present at the end of operation in all cases and during the operation in three cases.

(2) This degree of paralysis was constant, remaining throughout the operation and was unaffected postoperatively by any treatment given.

(3) The respiration was typical of a patient to whom a relaxant has been given. It was wholly diaphragmatic with a tracheal tug and of an amplitude insufficient to maintain respiratory exchange.

(4) The blood pressure was normal at the end of operation but fell a variable time after. Noradrenaline was ineffective in counteracting the fall.

Hunter (1956) has reported a series of six cases presenting a similar syndrome.

TABLE I

Case No	Diagnosis	Age	Pre-operative condition	Dosage of d-tubocurarine	Time of survival after d-tubocurarine
1	Strangulated umbilical hernia	69	Poor	25 mg	7 hr 15 min
2	Strangulated umbilical hernia	68	Poor	15 mg	2 hr 10 min
3	Strangulated femoral hernia	75	Poor	15 mg	3 hr 25 min
4	Strangulated femoral hernia	81	Very poor	10 mg	8 hr 15 min

TABLE II

Postmortem findings.

Case No	Heart	Lungs	Liver	Kidneys
1	Hypertrophy of left ventricle	Extreme oedema	Large, soft and fatty	Normal
2	Hypertrophy of right ventricle	Oedema upper lobes. Chronic bronchitis	Pale greasy	Mild pyelitis, otherwise normal
3	Muscle pale and soft	Oedematous	Advanced cloudy swelling	Slightly granular
4	Normal	Chronic vesicular emphysema. Oedema	Fatty	Normal

Foster (1956) has also reported a series presenting a slightly different picture. In his cases larger doses of d-tubocurarine were given and the blood pressure fell earlier.

As the cases quoted by Hunter received depolarizing relaxants as well, many people have cited the mixture of depolarizing and nondepolarizing relaxants as the cause of the respiratory failure.

As three out of four of the cases in this series quoted above and four out of five in Foster's series received only nondepolarizing relaxants it might be thought that it was indeed this group of drugs responsible for the respiratory failure in Hunter's series.

Hunter believes that depletion of potassium may be responsible for the syndrome, but treatment with potassium had at the most led to a transient small improvement.

Foster also believes that potassium depletion is aetiological but postulates a central effect. He suggests from clinical and experimental evidence that the central effects of d-tubocurarine are greater in potassium depletion. In the case he quotes as being typical, a woman received 70 mg of d-tubocurarine and slept for several hours postoperatively. A normal dose of neostigmine restored her peripheral muscle power but did not wake her. The irreversibility in certain cases is explained by the further penetration of d-tubocurarine into the axon where its effect is irreversible. For this penetration to occur he suggests there must be gross disruption of the normal barriers.

There are certain cases where a dramatic improvement of the muscle power is manifest after administration of potassium. They are the cases where the complete respiratory pattern returns but the muscle power is small.

The cases described above do not appear to fall into this category. Most cases of intestinal stasis and obstruction have some alteration in the blood chemistry and may have a low serum potassium, but the majority of cases show no abnormal reactions to relaxants. Most of these cases were poor risks but not desperately ill. They were not the cases with the most abnormal blood chemistry. They were patients who were expected to recover.

The cause of the irreversible paralysis may be in the neuromuscular junction and may not be directly related to potassium.

These cases do not appear to be myasthenic in type as a normal dose of d-tubocurarine produced a normal response, some muscle fibres being spared.

Neostigmine had no effect even in large doses.

Beecher and Todd (1954) showed in their survey that deaths in anaesthesia were five to six times as frequent with relaxants as without. They also showed that the skill of the anaesthetist did not alter the mortality rate. They found the death rate in poor risk patients was 1:96 with curare and 1:560 without. They were unable to offer an explanation for these figures and did not state the type of case which succumbed. They stated that 63 per cent of the curare deaths were due to respiratory failure and 37 per cent were due to cardiovascular failure despite adequate respiration.

Hodges and Harkness (1954) showed that the serum cholinesterase level was generally lower in poor risk patients although a constant variation was not obtained. Calloway et al. (1951) showed correlation between serum cholinesterase and cellular cholinesterase (as measured by red blood cell cholinesterase) so that a low serum cholinesterase is indicative of total low cholinesterase value in the body. McCance (1950) showed that in states of starvation the cholinesterase level fell; serum cholinesterase fell faster than cellular cholinesterase but a significant fall of both occurred. Waterlow (1950) and Hutchinson et al. (1951) also showed that cholinesterase was low in malnutrition. Vorhaus (1950) found a low cholinesterase in liver disease.

No cholinesterase estimations were done on these patients, but as they were all poor risk patients suffering from relative starvation and had liver changes it would not be surprising if their cholinesterase values were reduced.

The following explanation is offered for the irreversibility of the curare. It has been shown that the physically fit have a higher true cholinesterase than average (Calloway et al., 1951). It has also been shown that ill patients have a very low cholinesterase. In the fit person muscular responses are quicker, of greater power and more sustained than in the very ill. It is known that there is a constant leakage of acetylcholine at the myoneural junction,

causing subthreshold stimuli at the muscle end-plate (Fott and Katz, 1950).

Acetylcholine at the myoneural junction is broken down by cholinesterase. It is interesting to note that in highly trained soldiers, whose muscle tone is high, there is a high level of true and plasma cholinesterase. It is reasonable to presume that the production of acetylcholine is also at a high level.

It is believed that the cholinesterase level in different muscles is variable, being highest in the diaphragm and that the acetylcholine level is also highest in this muscle (Harris, 1951). In the ill patient the cholinesterase level may be very low. If, in these patients, acetylcholine were produced at a normal level, hypertonicity of muscles and excessive autonomic stimulation would be expected. In fact, the opposite is seen with poor muscle tone and depressed autonomic activity. Therefore it may be postulated that in these cases the whole of the acetylcholine-cholinesterase system is depressed.

If the production of acetylcholine at the myoneural junction is very depressed then the time necessary for a quantity to be produced, sufficient to overcome the curare block, may be very great, acetylcholine being unstable even in the absence of cholinesterase.

Anticholinesterases cannot be expected to help if the cholinesterase level is very low. Large doses of neostigmine may itself cause a central depression.

The cause of the depressed production of acetylcholine may be either (1) shortage of substrate, either choline or acetylcholine precursor, or (2) shortage of enzyme choline acetylase.

The blood choline level is depressed in starvation. Choline shortage predisposes to fatty liver; three out of four of these cases had fatty liver.

The characteristic respiration may be explained by the fact that only the central fibres of the diaphragm are working and these fibres are believed to produce more acetylcholine than any other muscle fibres (Harris, 1951).

The transient improvement in some cases brought about by the administration of potassium may be explained by the action of the potassium on those few fibres still working, the final depression being muscle fatigue.

Features causing the terminal circulatory failure.

(A) Autonomic blocking effect of d-tubocurarine.

This is not usually very great when small doses are used, and, as the blood pressure was maintained in the early part of all cases, it can largely be discounted.

(B) Diminished venous return from loss of muscle tone.

With reduced muscle tone a certain amount of venous pooling occurs. There was compensation at first with the maintenance of blood pressure. Compensation entails active constriction of arteries and a consequent increase in the work performed by the heart.

(C) Removal of negative intrathoracic pressure.

Maintenance on intermittent positive pressure ventilation entails an alteration in normal haemodynamics. This is usually compensated for by a rise in venous pressure. This compensation is only poorly maintained in very ill and elderly patients (Maloney et al., 1951). This is the process believed responsible for the circulatory failure in some of the patients in the poliomyelitis epidemic in Denmark (Pask, 1955).

The sudden drop in blood pressure was clearly due to primary heart failure explaining the pulmonary oedema present in all cases. This was a central failure of the circulation and no response to vasopressor drugs could be expected.

Maintenance of respiration by a mechanical respirator capable of giving a negative phase of respiration might have helped to maintain the circulation longer in these cases, but unfortunately such an apparatus was not available at the time.

Whatever may finally be established as the cause of this syndrome, one indisputable fact has emerged.

In certain patients with intestinal obstruction or stasis the effects of nondepolarizing relaxants will be fatal. As it is not possible to pick out the individual who will react in this way it is wiser to use no relaxants on this class of patient.

I have avoided this complication during the last eighteen months by the use of an alternative technique. My preference is cyclopropane and oxygen but I feel that in these cases the old maxim must apply that the technique most familiar to the administrator is the safest.

I have had cholinesterase estimations performed on the obstructions who have been ill for more than twenty-four hours. Only one has had a very low cholinesterase and he was successfully anaesthetized with the rest, using cyclopropane.

There is need of further investigation into this type of reaction. If such cases occur in the future, I suggest that the following investigations may yield valuable information:

(1) Blood chemistry especially potassium levels.

(2) Serum cholinesterase and choline levels.

(3) The reaction of the muscles to stimulation of nerve trunks. This would differentiate between central and peripheral depression.

Treatment.

Until the aetiology has definitely been established, all routine drugs must be tried. Potassium does seem to help the occasional case. The administration of choline may have a place if the blood choline level is greatly reduced.

SUMMARY

Four cases of acute intestinal obstruction are reported, all of whom died from the irreversible paralysis produced by d-tubocurarine. All these cases were at first believed to be deaths due to toxaemia but on review they appear to present a different syndrome. Death was due to primary respiratory failure, and circulatory failure was only a terminal event. In toxaemia the reverse is expected, that is primary circulatory failure and terminal respiratory failure. An explanation is offered for the unfortunate sequence of events.

ACKNOWLEDGMENT

I would like to acknowledge my indebtedness to the surgeons and anaesthetists concerned for permission to publish these cases.

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PROLONGED RESPIRATORY DEPRESSION FOLLOWING SUXAMETHONIUM CHLORIDE DUE TO A DUAL BLOCK

BY

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MANY cases of prolonged apnoea or deficient ventilation following the use of suxamethonium and other short acting depolarizing muscle relaxants have now been reported. Several theories have been advanced to explain the unexpectedly prolonged action of a drug which in the average individual in average doses has a duration of action of only a few minutes. Evans et al. (1952) showed that in the case of suxamethonium chloride (Scoline) prolonged apnoea could be correlated with a low plasma pseudocholinesterase level and inferred that duration of activity could be predicted from the pseudocholinesterase level. However, many cases of prolonged apnoea have occurred in patients with normal levels of plasma pseudocholinesterase.

Paton (1953) and Zaimis (1953) have both noted that a dual type of myoneural block may occur in some animals when decamethonium or suxamethonium were used, in which an initial depolarization effect was followed by a competitive or nondepolarizing neuromuscular block. This type of action is seen in myasthenics given decamethonium, and it would appear that in all situations of this kind the depolarizing drug comes to lose its characteristic action and becomes additive with competitive drugs and reversible by anticholinesterases. Churchill Davidson and Richardson (1952, 1953) have described a " dual " type of response in humans with myasthenia which is attributable to changes in the motor endplates and not to a change in the chemical composition of the depolarizing drug in the body.

Brennan (1956) found that in 62 cases neostigmine 2 mg given to normal patients who had received suxamethonium chloride (150–950 mg) by intravenous drip usually had an antidotal effect as demonstrated by respiratory muscular activity, whereas a dose of 10 mg of gallamine usually had an additive effect. This would suggest that, especially when large doses of suxamethonium have been used, a dual block occurs, and further that where prolonged apnoea follows even a moderate dose by single injection of suxamethonium, the likelihood of a dual block is present and steps should be taken to confirm this and possibly reverse it. Brennan believes that the dual action exerted by succinylmonocholine is not important clinically, since the amount of the monocholine necessary to exert any effect would derive from the breakdown of far more suxamethonium than is ever used in anaesthetic practice.

The following case of prolonged apnoea following suxamethonium chloride was successfully dealt with on lines suggested by Brennan.

Case Report.

A stout woman, aged 42, weight 9 st. 5 lb. (59 kg), adjudged a good anaesthetic risk, underwent a cholecystectomy for cholecystitis. Premedication: papaveratum 20 mg hyoscine 0.4 mg.

a.m.

9.10 Induction: thiopentone 350 mg; suxamethonium 100 mg.
The patient was ventilated with oxygen and a No. 9 cuffed endotracheal tube passed without difficulty. Anaesthesia was maintained with nitrous oxide and oxygen (5 l.:2 l.) in a closed circuit (Marrett) with a leak. Fresh soda lime was used.

9.15 Apnoea persisting. Respiration controlled.

9.25 Operation commenced.
Apnoea still present; patient fully relaxed. Absorber cut off for a while and carbon dioxide allowed to accumulate with no effect on respiration.

10.10 Patient still apnoeic.
Sample of blood taken for plasma pseudocholinesterase estimation.

10.15 Respiration just perceptible; rate 40/min.

10.20 Pethidine 20 mg in water 2 ml given intravenously as movement of fingers was noticed.

10.25 Respiration slower 28/min, but depth still inadequate. Operation completed.
10.28 Slight improvement in depth of respiration, but still only diaphragmatic. Ventilation poor. Gallamine 10 mg given. Apnoea resulted within a minute. Atropine 1.2 mg intravenously.
10.33 Neostigmine 1 mg given. Respiration soon resumed, 20/min; inadequate but improving.
10.36 Neostigmine 1 mg given. Ventilation now much improved.
10.40 Neostigmine 0.5 mg given. Anaesthetic withdrawn and endotracheal tube removed. Patient coughed.
10.50 Respiration satisfactory. No tracheal tug. Consciousness returning. Colour good, returned to ward.

Postoperative course was uneventful. The plasma cholinesterase level subsequently proved to be low, 23 units (normal 40–100 units).

DISCUSSION

Depressed respiration or prolonged aponea following anaesthesia in which a depolarizing relaxant has been used may be due to:

(1) The various causes of central respiration depression, such as overdose of anaesthetic or analgesia drug or errors of ventilation.
(2) Overdose of or susceptibility to the relaxant drug still acting as a depolarizing agent.
(3) A change in response of the motor endplate and the onset of dual block of prolonged duration.

In the case mentioned above apnoea lasted 65 minutes and ventilation was grossly inadequate for a further 15 minutes. The dose of thiopentone (350 mg) which was given was considered too small to have any marked central effect. The plasma cholinesterase level was low but this was not known at the time and would have been confusing if it had been. Adequate controlled respiration was given throughout the operation. Carbon dioxide was, however, allowed to build up on several occasions to exclude over ventilation as a possible cause of respiratory depression. The dose of suxamethonium given (100 mg) was large, but a depolarizing block lasting more than 10 minutes was not to be expected. The fact that gallamine 10 mg increased the respiratory depression at the end of operation and that neostigmine 2.5 mg completely reversed the condition implied that a nondepolarizing block had supervened upon the original depolarizing block.

It has previously been suggested that a single dose of a depolarizing drug produces a pure depolarization block except in myasthenia gravis, and that it is only after repeated doses or continuous infusion that a change in the response of the motor endplate occurs with a resulting nondepolarizing block (Churchill Davidson, 1956). In this case suxamethonium was given in a single dose and yet all the evidence suggests that a dual block had in fact occurred.

It is probable that many reported cases of prolonged respiratory depression following the use of the depolarizing relaxant drugs have been due to the dual blocking effect, but other factors may influence the action of neuromuscular blocking agents; these are not fully understood but a few examples may be mentioned. The ionic environment at the motor endplate and muscle membrane may condition the response to relaxants (Paton, 1956). Defect of liver function may affect the response to relaxants by producing a low serum potassium level (potassium is mobilized from the liver by adrenaline) rather than by producing a low plasma cholinesterase level. Increased carbon dioxide tension may affect neuromuscular transmission. Whereas Scurr (1954) suggested that hypercarbia may prolong a depolarizing block or produce a neuromuscular block, Payne (1956) working with cats has shown that hypercarbia tends to reduce the blocking effect of suxamethonium. The result of further investigation on the effect of carbon dioxide tension on neuromuscular transmission is awaited with interest. Paton (1956) also has re-emphasized the uncertainty of action of neuromuscular agents when for example a depolarizing drug is followed by a nondepolarizing one, before the former has been broken down or eliminated from the body.

This case illustrates that having excluded respiratory depression due to thiopentone, pethidine, morphine or other drugs, steps may be taken to ascertain whether a dual block has resulted from the administration of suxamethonium. Gallamine in small doses will potentiate a dual block and should have little effect on or antagonize a pure depolarizing one and is a safe test, following which neostigmine should rapidly reverse a dual block. Edriphonium (Tensilon) given without the gallamine test has a sufficiently brief action to be safe as an alternative therapeutic test, though it potentiates a depolarizing block.

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CORRESPONDENCE

FLUOTHANE AND THE BOYLE VAPORIZER

Sir,—I should like to congratulate Dr. Falkner Hill on his timely and comprehensive report on the percentages of Fluothane vapour delivered by the Boyle vaporizer. This work will provide valuable guidance to those using Fluothane and it gives ample warning of the pitfalls likely to be met when using such a potent anaesthetic agent (Raventos, 1956) in a vaporizer designed for much weaker agents. Some months ago Dr. Hill very kindly granted me access to his charts for the use of Fluothane in the ordinary standard Boyle vaporizer (smaller bottle). One thousand cases have now been successfully completed with the 10 litre flow method and 300 with the 3 or 4 litre flow method.

The 10 litre gas flow with a calibrated vaporizer initially set to give 2 per cent Fluothane —room temperature, lever $\frac{1}{4}$-on, and plunger fully withdrawn—has given very smooth anaesthesia for prolonged periods in spite of the decline in vapour concentration as the temperature and volume of the Fluothane liquid fell with vaporization. This progressive fall in vapour concentration is associated with the disappearance of the vascular hypotension induced in a proportion of cases by the initial 2 per cent Fluothane vapour, the blood pressure returning to near normal levels in around 5 minutes.

On using vaporizers which had not previously been calibrated it was observed that the $\frac{1}{4}$-on lever setting gave rather irregular results, some vaporizers giving too much, others too little. This inconsistency became particularly obvious when using the 3 or 4 litre flow method and necessitated the control of anaesthesia by clinical signs rather than by the use of known vapour concentrations. Owing to the very low vapour concentration of Fluothane needed for anaesthesia, leakages in the equipment create considerable difficulty in obtaining adequate anaesthesia, the commonest faults being a missing or damaged bottle washer, an inefficient expiratory valve, or a badly fitting face mask.

The disadvantage of the 10 litre flow technique is that it uses Fluothane most extravagantly. This disadvantage has been largely eliminated by using low gas flows in conjunction with carbon dioxide absorption by soda lime. This method can easily be applied by means of the Waters " to and fro " absorption technique. With gas flows of 3 or 4 litres a minute the $\frac{1}{4}$-on lever setting has been more or less satisfactory, but the plunger should be kept not more than 2 cm above the surface of the Fluothane in the bottle. It should be noted that Dr. Hill's graphs of 3 litres a minute were obtained from a modified vaporizer; essentially similar conditions are obtained in the standard vaporizer by keeping the plunger 2 cm above the surface of the liquid. As already mentioned, this technique does not give consistent results with uncalibrated vaporizers and it is sometimes necessary to move the lever above or below the $\frac{1}{4}$-on mark to obtain satisfactory conditions. It tends to give a somewhat deeper plane of anaesthesia, and respiratory depression and hypotension are more frequently encountered than with the 10 litre flow technique; with experience the respiratory and

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CITRATE INTOXICATION FOLLOWING A RAPID MASSIVE BLOOD TRANSFUSION

BY

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THE technique of rapid intravenous transfusion has become routine in the treatment of massive haemorrhage and severe shock and has so far not resulted in ill effects.

The following case is of interest in that the rapidity of transfusion of a large volume of bank blood would appear responsible for an instance of ventricular fibrillation.

CASE REPORT

A woman of 27 weighing 60 kg was submitted to surgery for Fallot's tetralogy. She had been an invalid all her life and was unable to walk more than a few steps. At operation dilatation of the pulmonary valve and punch excision of an infundibular stenosis was performed via the left pulmonary artery. This operation was uneventful apart from some considerable blood loss both from the pulmonary artery and from some pleural adhesion at the apex of the left lung. During the operation 1080 ml of blood were given, the second bottle still running on her return to the ward.

Two and a half hours later, as she was being sat up, the intercostal drain suddenly delivered 440 ml of almost pure blood and continued so to drain for the next 6 hours. Altogether in the 10 hours following her operation 1100 ml of apparently pure blood had drained into the leak bottle and 1620 ml of blood had been replaced. Radiographic studies of the chest revealed a complete haemothorax.

Her general condition at this time remained good; the blood pressure and pulse being steady, it was decided that the chest should be re-opened. On return to the theatre, however, her general condition had deteriorated considerably. The pulse was practically impalpable and the blood pressure unrecordable. This situation responded well to a rapid transfusion of blood with a Martin pump and the chest was re-opened. After removing a large quantity of fresh clot the heart was observed to be in normal rhythm, in which state it remained for the next 20 minutes.

During this time a large quantity of blood was transfused, 2700 ml in all, and the general condition was improving steadily. No obvious bleeding point was found; the pulmonary artery was secure but there was considerable oozing from the raw lung surface at the left apex.

Twenty minutes after the commencement of the operation the heart, which had been in normal rhythm, suddenly entered ventricular fibrillation. The use of a defibrillator and intracardiac neostigmine failed to restore normal rhythm, but as a large quantity of blood had been transfused, citrate intoxication was considered. 2 ml of 10 per cent calcium chloride were given intracardially and the heart was immediately restored to normal rhythm.

Although cardiac massage had been maintained throughout the period of fibrillation, and despite the use of hypertonic sucrose solution, the patient died 48 hours later as a result of cerebral damage, presumably accounted for by the 8-minute period of fibrillation.

DISCUSSION

The sudden change from normal rhythm to ventricular fibrillation would seem worthy of comment. The circulation had been restored and was maintained by rapid infusion. At all times a high concentration of oxygen was administered, and there had been no undue handling of the heart. The reversal to normal rhythm following calcium chloride is significant. During the previous 20 minutes 2700 ml of bank blood had been infused. This fluid contained 2100 ml of blood, 500 ml of 2 per cent disodium citrate and 50 ml of 15 per cent dextrose solution. Thus 10 gram molecules of disodium citrate had been infused in 20 minutes. Mollison (1951) states that the harmful effect of citrate infusion will not be seen unless the dosage exceeds 250 mg/kg/hour, and in this case approximately 500 mg/kg/hour had been given.

Shafer (1936) attributes the toxicity of citrate to its ability to lower the free Ca ions thus producing paralysis of the cardiac vagus, and Shafer and Crisman (1936) have shown that this effect takes place more readily in animals that have been bled: so that protection may be obtained by the prophylactic use of calcium.

During the storage of blood, potassium passes out of the cells into the plasma and after storage

for 10–14 days the level of potassium in the plasma of stored blood is between 80 and 100 mg/100 ml (Loutit, Mollison and Young, 1943). The blood used in this case was all reasonably fresh and under 10 days old and approximately 900 mg of potassium were therefore given in 20 minutes. DeGowin, Hendin and Harris (1940) administered 473 mg of potassium in 12 minutes and were unable to demonstrate electrocardiographic changes, and only a small rise in serum potassium. It would seem, therefore, that the potassium content of the blood transfused was not unduly high.

In replacement therapy in infants for haemolytic disease of the newborn, it is customary to remove part of the supernatant fluid and to give calcium in order to minimize these toxic effects from the stored blood (Mollison, 1951), and it would seem a useful precaution, when massive rapid transfusion is contemplated, that a source of free calcium ions be used as a prophylactic measure against the occurrence of citrate toxicity. Ten per cent calcium gluconate solution provides such a free source and when such transfusions are given, may be added to the blood being transfused. In paediatric practice 1 ml per 100 ml of blood transfused is added, but in these larger transfusions 10 ml of calcium gluconate per 1500 ml of blood transfused is an easy way of providing this free source of calcium ions.

SUMMARY

A case of citrate toxicity following rapid massive whole blood transfusion is described.

It is suggested that a source of free calcium ions be provided when such a transfusion is used.

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vascular effects can be easily controlled. The only circumstances in which respiratory depression has interfered seriously with the induction and maintenance of adequate anaesthesia have occurred when respiratory depressants such as papaveretum or the longer acting barbiturates have been given pre-operatively.

The Boyle vaporizer has already been condemned as dangerously obsolete when used with trichloroethylene (Gilchrist and Goldsmith, 1956). When I started to use Fluothane in this vaporizer I must confess that I was at times rather disconcerted by the sudden and profound changes in the depth of anaesthesia which often followed alterations in the lever position of as little as 0.3 cm. With increasing experience, however, it soon became possible satisfactorily to control the vaporizer and since then, both in the operating theatres and in the recovery rooms, Fluothane has consistently given me results incomparably better than any I have ever obtained with other agents and techniques; at the time of writing over 1,300 patients have been anaesthetized, the operations and anaesthetic technique being essentially similar to those already reported (Johnstone, 1956) with the exception that pure oxygen has been used in the low flow technique. I am convinced, however, that, if accidents and misconceptions are to be avoided, it will be necessary to introduce a standard vaporizer. This means vaporizers so carefully made and delicately calibrated that they can be changed without loss of accuracy.

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QUICK FITTING ENDOTRACHEAL ADAPTERS

BY

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THE present drive to eliminate the hazards of static electricity in the operating theatre has greatly increased the nuisance value of most endotracheal adaptors in common use.

Ordinarily it is an easy matter to make a gas-tight fit between the bulbous end of the union and the tubing of the catheter mount. Antistatic rubber, however, is less distensible, and a certain amount of manoeuvring, lubrication, and ingenuity may have to be exercised before the connecting tubing is coaxed on to the adapter.

On the other hand, if the tubing slides easily into place, the loss of elasticity, which is associated with the antistatic rubber, may interfere with its gripping power, and an insecure joint results. The disadvantages of such a situation are obvious, especially in surgery of the head and neck, where the operation may have to be stopped, while the anaesthetist remakes the connection and secures it with adhesive plaster or other means. A real danger of anoxia, before the broken junction is discovered and rectified, exists in the curarized patient; nor does an elementary mechanical failure of this nature help relations with the surgeon.

We therefore felt that a modification, dispensing with this rubber-metal connection, might be useful and a description follows of three adapters which employ a metal to metal joint.

The Adapters (fig. 1).

These instruments are of the conventional T-shaped pattern, the vertical limb consisting of a suction funnel above the ridged section for the endotracheal tube, while the horizontal segment contains the joint. The assembled unions measure 44 mm vertically and 30 mm in the horizontal limb.

In use a tight fit is made between the bulbous end of the adapter and the tubing of the catheter mount. This segment of the union now forms a permanent part of the mount, which is in future attached to the vertical limb by making the metal joint. This latter limb of the union, which accurately fits the catheter mount segment, is in four sizes to accommodate the varying bore of the endotracheal tubes.

FIG. 1

A. Endotracheal catheter mount.
B. Endotracheal catheter mount with the mount segment of the "cone joint" union in position.
C. The mount segment of the "bayonet-clip" union.
D. The mount segment of the "hosepipe" union.

The "Cone Joint" Union (fig. 2).

This is the simplest of the adapters to be described. The male part of the joint is carried on the catheter mount and is held by friction in the corresponding female cone. We have made this joint rather long to offset the pull of the corrugated breathing tubing, the male truncated cone being 15 mm in length.

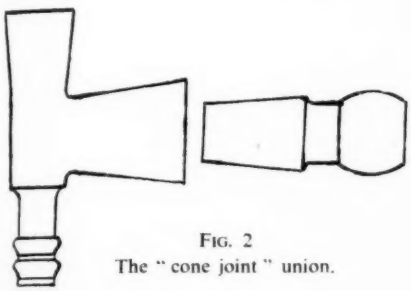

FIG. 2
The " cone joint " union.

The " Bayonet-Clip " Union (fig. 3).

Variations on this type of joint are commonly found in medical instruments and the locking arrangement is typified by that of the Labat syringe for local anaesthesia. The female cone on the bulbous end of this adapter is forced tightly on to the male component of the joint by the screwlike drive of its tapering flange.

The " Hosepipe " Union (fig. 4).

This connection employs a modification of the joint used to cement lengths of fire-hose together. The slight screw arrangement of the flanges on the catheter mount segment forces this part of the union against the endotracheal limb, thereby locking the joint.

Although other forms of metal junctions were investigated we considered that these three were most easily applicable to the problem of endotracheal unions.

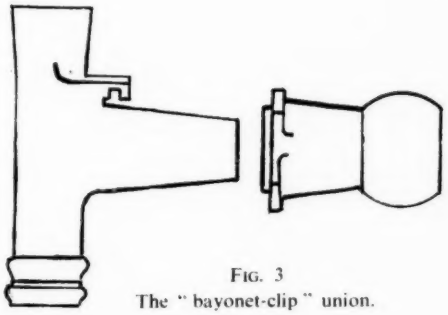

FIG. 3
The " bayonet-clip " union.

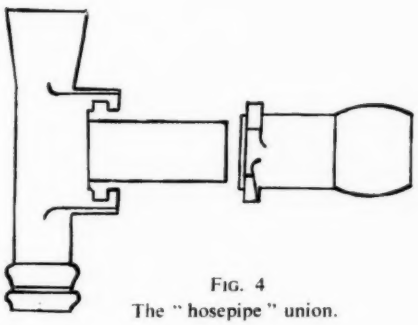

FIG. 4
The " hosepipe " union.

ACKNOWLEDGMENTS

Our thanks are due to Major J. H. Watson, R.E.M.E., for his technical advice and to Herr S. Homberg for making the instruments.

ASSOCIATION OF ANAESTHETISTS OF GREAT BRITAIN AND IRELAND

JUBILEE MEETING

The Association of Anaesthetists of Great Britain and Ireland is celebrating the twenty-fifth anniversary of its formation this year, and is holding its Annual Meeting on December 4, 5, 6 and 7, 1957, at the Royal College of Surgeons, Lincoln's Inn Fields, London, W.C.2.

The provisional programme is as follows:

Wednesday, December 4
Evening: The Association will hold a Cocktail Party to welcome those overseas visitors who will attend the meeting.

Thursday, December 5
Morning session: Papers.
Afternoon session: Annual General Meeting. Frederic Hewitt Lecture.
Evening: Annual Dinner.

Friday, December 6
Morning Session: Papers.
Afternoon session: Papers. Meeting of the Section of Anaesthetics of the Royal Society of Medicine.
Evening: Cocktail Party given by the Faculty of Anaesthetists. Dance.

Saturday, December 7
Morning session: Symposium.

Throughout the Meeting there will be a Scientific Exhibition and a Trade Exhibition.

The final date for submission of papers for presentation at this meeting is June 1, 1957.

Further particulars will be available later on application to the Secretary, Association of Anaesthetists of Great Britain and Ireland, 45 Lincoln's Inn Fields, London, W.C.2.

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MODIFICATIONS TO THE STANDARD RUBBER FACE MASK FOR USE WITH BABIES AND SMALL CHILDREN

BY

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THE commonest form of arrangement of anaesthetic apparatus used in adult surgery in this country is that shown in figure 1. It comprises a Boyle's machine, having a reservoir bag interposed between machine and corrugated delivery tubing, with a Heidbrink type expiratory valve near the facepiece.

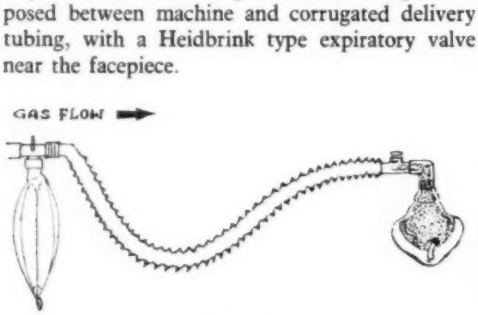

FIG. 1

Measurements with this assembly show that the effective dead space (indicated by shading) may be easily as much as 150 ml, and this cannot be reduced much below 100 ml even when employing a small child's pattern rubber face mask.

With a tidal volume of 500 ml or more, as is commonly to be found in adults, this does not in practice seem to constitute a hazard, although on theoretical grounds, any increase in physiological dead space is to be avoided.

In children, tidal volumes under resting conditions fall much below the adult figure, and Hall (1955) has shown that the resting tidal volume in an eight-year-old child does not normally exceed 230 ml, whilst at the age of two years, the figure is as low as 150 ml. It follows, therefore, that use of the adult type of assembly in paediatric anaesthesia will inevitably be associated with rebreathing, leading to a progressive accumulation of carbon dioxide, and even to hypoxia.

A further objection to the adult assembly lies in the fact that the expiratory valve itself will probably have a resistance of from 1.0 to 6.7 cm of water before it opens, using a flow rate of 5 litres/minute and with the valve screw in the open position (Mushin and Mapleson, 1954). Any resistance to expiration must entail a rise in pressure in the respiratory tract, leading to an increase in functional residual air and thus to an increase in dead space (Mushin and Rendell-Baker, 1953).

For these reasons, therefore, it is customary in paediatric work either to use a completely open technique, such as ethyl chloride and ether on a gauze covered wire mask or, if the Boyle's machine is to be used, first to intubate the infant or child, and then to use a nonrebreathing technique employing Ayre's T-tube. Frequently in the latter case, the need for intubation is dictated entirely by the necessity of avoiding an increase in the dead space.

A method has accordingly been devised whereby the anaesthetic machine may be used even on the smallest infant without recourse to intubation, and this is illustrated in figure 2.

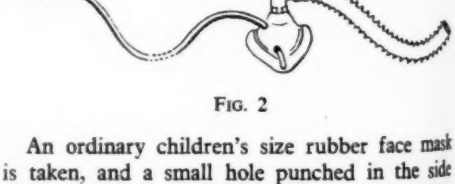

FIG. 2

An ordinary children's size rubber face mask is taken, and a small hole punched in the side of it, near to the normal gaseous inlet hole. Through this is threaded from the inside a small metal tube having a flange on one end. This

flange comes up against the inner surface of the rubber and prevents the tube being forced right through. The author actually uses for his flanged tube a spare Magill oral endotracheal connection size No. 2 and has found it to be quite satisfactory. Enquiries are, however, being made of surgical instrument manufacturers as to whether it would be worth while making a special tube having a thread and nut to hold it more firmly.

The incoming gases are led in via the flanged metal tube, being conveyed from the machine by pressure tubing of moderate bore. Expired gases are allowed to escape via the normal route, employing an angle piece and short length of corrugated tubing (about 12 inches). Flow rates employed are similar to those used with Ayre's tube and an endotracheal catheter, and are usually up to about 7 litres/minute of nitrous oxide and oxygen, usually in conjunction with ether.

It will be found that the same medium size face mask may be used even when anaesthetizing neonates, as a perfect fit is not essential. Thus there is no need to modify more than one mask, although the altered mask may in fact be restored to normal by the application of a small piece of adhesive tape over the hole.

The author has employed this modified mask in neonates, using cyclopropane and oxygen in flow rates of 500 and 1,000 ml per minute respectively, and has found it particularly useful in cases of hypertrophic pyloric stenosis. For operations of short duration, such as Rammstedt's, it is felt that the expense of using cyclopropane is justified, and the explosion risk is no greater than with open ether.

ACKNOWLEDGMENT

I wish to express my thanks to Dr. A. R. Hunter for his helpful advice, and also to Dr. Badola for the illustrations.

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INTERNATIONAL SYMPOSIUM ON CURARE AND CURARIZING SUBSTANCES

A symposium dealing with curare and curarizing substances will take place in Brasil from August 5 to 17, 1957.

The organizing bodies are UNESCO, the Conselho Nacional de Pesquisas (National Council of Research Brasil), the Academia Brasilera de Ciencias and the Universidade do Brasil (Rio de Janeiro), and the symposium is under the Patronage of the President of the United States of Brasil.

The meetings will be held between August 5 and 10 at the University of Brasil in Rio de Janeiro and will consist of a series of reports and communications on (*a*) the ethnographic problems concerning South American curares, (*b*) the botanical origin of the active principles of curares, (*c*) the chemistry of the curarizing alkaloids, (*d*) synthetic curares, (*e*) physiology of neuromuscular transmission and mechanism of curarization, (*f*) pharmacological properties, (*g*) clinical application of curares.

The official languages of the Symposium are Portuguese, English, French and Spanish.

The papers presented will subsequently be published by UNESCO, and the Paternò Foundation of the Istituto Superiore di Sanità, Rome.

All correspondence should be addressed to Prof. C. Chagas, Instituto de Biofisica, Universidade do Brasil, 458 Avenida Pasteur, *Rio de Janeiro*, and for Europe to Prof. Daniel Bovet, Istituto Superiore di Sanità, 299 Viale Regina Elena, *Rome*, and also to Prof. P. B. Carneiro, Délégation du Brésil, UNESCO, 19 Av. Kléber, Paris 16ème.

ON CHLOROFORM AND OTHER ANÆSTHETICS

THEIR ACTION AND ADMINISTRATION

BY

JOHN SNOW, M.D.

Licentiate of the Royal College of Physicians

(*Continued from page* 96)

SYMPTOMS IN THE FATAL CASES OF INHALATION OF CHLOROFORM

Out of the fifty cases of death from chloroform, related above, there are five in which the symptoms at the time of death are not detailed, viz., Cases 6, 7, 21, 24, and 50; in the two first cases it is merely related that the patient suddenly expired and, in the two last cases, no one was watching the patient at the time when death took place. In considering the remaining cases they may be conveniently divided into groups, according to the period of the inhalation at which the accident occurred. In six of the cases the fatal symptoms came on suddenly, at the beginning of the inhalation, before the patient had been rendered unconscious; in each of these cases there was the most unequivocal evidence of the sudden arrest of the action of the heart. In cases No. 4 and No. 11 there was sudden pallor of the face at the moment when the circulation ceased. In Nos. 14 and 26 the face became livid at the time of the fatal attack, and, in Nos. 45 and 46, the colour of the face is not mentioned. In all these cases there were also symptoms as if of a sudden shock to the system, such as stretching out of the limbs, foaming at the mouth, rolling of the eyes, or a sudden convulsive start. In Case 4, the patient at Boulogne had just complained of a choking feeling, one sign that the vapour she was breathing was not well diluted. In Case 11 the fatal symptoms occurred immediately on a full inspiration; and in the other cases also the strength of the vapour was left to accident, and the result leads to the conclusion that it was very great at the moment before the fatal symptoms occurred.

In thirteen cases the inhalation was discontinued on account of the sudden appearance of dangerous symptoms, after consciousness had been apparently suspended. These cases are numbered, 9, 15, 17, 20, 27, 30, 33, 35, 37, 40, 41, 44 and 47. In the greater number of these cases the overaction of the chloroform appeared to be exerted simply on the heart, the only dangerous symptoms being referrible to the paralysis of that organ; whilst in some of these cases symptoms of over narcotism of the brain were conjoined with those connected with the heart. In the case of J. Verrier, No. 9, and in the case at Stockholm, No. 15, the sudden and entire cessation of the pulse was the symptom which first called attention to the danger of the patients whilst the breathing was still going on. In Case 30 the woman became suddenly insensible and pulseless, after a short period of excitement. In Cases 35 and 40, although the pulse did not absolutely and entirely cease at once, its sudden failure was the first alarming symptom. In Case 20, at the Cavan

Infirmary, the breathing and action of the heart ceased at the same moment. In Case 41, at the Middlesex Hospital, at a time when the pulse was full and steady, seventy in the minute, it gave a few rapid and irregular beats, and then ceased, and the breathing, which was free and deep, but not stertorous, ceased at the same time. In case 15, which occurred at Jamaica, the patient, after a period of excitement, made one stertorous inspiration, when the breathing ceased. There were afterwards a few distant inspirations. The pulse is not mentioned; but it is pretty certain that it must have ceased about the time of the stertorous inspiration or the additional inspirations which took place after the chloroform was withdrawn, would probably have restored the patient; to say nothing of the measures that were resorted to with a view to his resuscitation. Of Case 27, which happened at Melbourne, it is merely related that the patient spluttered at the mouth, and suddenly expired, just after a fresh portion of chloroform had been applied on the handkerchief. The symptoms of spluttering at the mouth is recorded as occurring in other cases, just at the moment when the pulse had suddenly ceased.

In Case 44, at the Royal Ophthalmic Hospital, the narcotism of the brain and nervous system proceeded as far as the third degree, which was attended with strong muscular spasms, as not infrequently happens; as an overdose of chloroform appears at this moment to have acted on the heart, for the pulse could not afterwards be felt. In Cases 33, 37, and 47, the narcotism of the brain proceeded as far as the fourth degree, producing stertorous breathing, when the chloroform caused paralysis of the heart, by its direct action on that organ.

There are six cases in which the fatal symptoms came on just after the patient had been rendered insensible, and the inhalation had been discontinued; the operation being about to be commenced. They are numbered 32, 34, 39, 43, 48, and 49. All these cases bear a very close resemblance to each other. In all of them the patient had been made insensible (satisfactorily so as it was thought), when in a few seconds the pulse suddenly stopped, or failed and fluttered just prior to stopping; in Case 32 Dr. Dunsmure thought the time was longer between the discontinuance of inhalation and the cessation of the pulse. The breathing continued a little time after the pulse ceased or failed in all these cases, and there was an absence of the spluttering at the mouth, stretching of the limbs, and other spasmodic actions, which occurred in all the six cases where the heart was paralysed at the beginning of the inhalation, before unconsciousness had been induced, and in some of those when the paralysis of the heart took place at a later period of the inhalation, when the patient had been apparently rendered unconscious, but was not yet insensible. In each of the six cases now under consideration, the fatal event was evidently occasioned by the vapour of chloroform, which remained in the lungs at the moment when the inhalation was discontinued. A portion of this vapour becoming absorbed, and added to that already in the blood, had the effect of paralysing the heart, when it circulated through the coronary arteries.

There remain twenty-two cases in which the fatal symptoms came on during

the course of the operation. In twenty of these cases the symptoms are described with more or less detail. I made some remarks respecting cases No. 1 and No. 2, in the place where they are related. In case No. 3, as in these cases, the patient appeared not quite insensible, and showed signs of pain during the operation, when "in a moment his pulse, which was full and natural, sank." In case No. 5 the patient was probably dead when the incisions on the finger were commenced; the extreme suddenness of the death, and the absence of bleeding, show that death occurred in the way of syncope. The convulsive movements which just preceded death are worthy of note in connection with the other cases, in which death occurred immediately after the commencement of inhalation. Some remarks were appended to case No. 8. In case No. 10 paralysis of the heart is indicated by the absence of bleeding from the arteries, and the absence of pulse, whilst the breathing still continued for a short time. I made some remarks respecting case No. 12 when it was related. The patient seemed to die by embarrassed respiration, but whether that was caused by the action of the chloroform on the brain is doubtful. In case No. 13 the patient died in a moment. In No. 16 the face turned pale, and the pulse and breathing ceased soon after the chloroform was discontinued, showing the effect of the vapour which was present in the lungs at the moment when the inhalation was left off.

In Case 18 the livid countenance and sudden stopping of the pulse prove cardiac syncope. In Case 19 the blood which was gushing out suddenly stopped, and the patient expired. The congested state of the lungs and the blood in the right cavities of the heart prove that the syncope of which he expired was not the ordinary anaemic syncope from haemorrhage; it was therefore cardiac syncope from the chloroform.

In Case 22 the change of countenance and sudden character of the death are evidences of cardiac syncope. In Case 23 there was a sudden cessation of the bleeding and of the pulse; in Case 25 the pulse suddenly ceased. In Case 28 the patient died suddenly, but the pulse was apparently not examined at the time. Some remarks have already been made on Case 29, which happened in the Manchester Infirmary. In Cases 31, 36, and 38 the suddenness of the death showed that it took place by syncope. In the last of these cases the pulse was being examined at the time it ceased. In Case 36 there was no examination of the dead body; but in 31 and 38 the presence of blood in the right cavities of the heart indicates that the kind of syncope was cardiac syncope. Respecting Case 42, some remarks have already been made. The death commenced by deep coma, which embarrassed, and then suspended, the respiration, and cardiac syncope quickly followed. The chloroform was administered by a method which precluded the medical attendant from observing properly the most important symptoms.

The accompanying table of the fatal cases of the inhalation of chloroform contains such short particulars respecting them as seemed capable of being tabulated, and it may assist the reader in retaining a more connected recollection of the facts previously related more in detail.

(*To be continued*)

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